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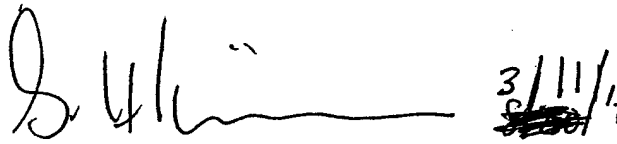

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Abstract

The purpose of this study was to determine: 1) the effects of the time of the menstrual cycle (luteal, ovulatory, & follicular) on the pharmacokinetics of three drugs which are leading candidates for fielding (caffeine, triazolam) or are currently fielded by the U.S. military (atropine) and an inactive intravenous marker (cardio-green); 2) The effect of the menstrual cycle on hepatic blood flow (cardio-green) and drug metabolism (caffeine); and 3) the effect of the menstrual cycle in combination with a stimulant (caffeine), a depressant (triazolam), and a chemical defense treatment (atropine) on a variety of pharmacodynamic (Hormonal, physiological, performance, etc.) responses.

To date, manuscripts have been published on the effects of the menstrual cycle on the pharmacokinetics of caffeine and on the pharmacokinetics of Cardio-green and triazolam. Statistical analyses of the performance (cognitive) data have been completed and manuscripts are in preparation for submission. A GC-Mass spec method for the measurement of atropine in human biological samples (e.g. blood) is under development, however sample analyses have not been completed due to lack of funding.

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Introduction

Gender has been shown to influence a number of pharmacokinetic variables including, serum protein binding (1), absorption rate (2), peak plasma concentration and area under the curve (3), and drug clearance (4). A number of factors may contribute to gender differences in drug disposition including, differences in body composition, the use of oral contraceptives, plasma levels of the sex hormones, and the phases of the menstrual cycle (5,6). To date very few studies have actually examined the effects of the time of the menstrual cycle (follicular, ovulatory, luteal) on the pharmacokinetics and concomitant pharmacodynamics of a drug.

At the present time females make up a significant proportion of the U.S. Army (about 12%). A variety of pharmacologic agents are currently fielded or are being considered for fielding by the U.S. Army. Fielded agents include intramuscular atropine, used as a treatment for nerve agent exposure. Drugs being considered for fielding include triazolam (halcion), a short acting sleeping agent, and caffeine, a well-accepted stimulant.

Modifications in the pharmacokinetics of a drug can in turn alter its pharmacodynamics and/or toxicological profile. If a drug is removed more rapidly from the body, normal dosing schedules may prove inadequate due to either a reduction in the residence time or inadequate concentration of the drug. Conversely, a decrease in drug removal or inactivation with no modification in its administration schedule may result in an undesirable increase in drug levels with a greater potential for a toxic reaction (7,8). A wide variety of environmental stressors have the potential to modify drug kinetics and dynamics. These include hypoxia (9), high altitude (10), exercise (11,12), and even sleep deprivation (13). Unfortunately, only a handful of studies have included women in the subject population.

A variety of hormonal and physiological changes associated with different phases of the menstrual cycle have the capacity to modify the kinetics and dynamic responses of drugs in premenopausal women. Limited research to date (4, 14-17) has identified changes in drug kinetics. However, these studies only examined one or two phases of the menstrual cycle (luteal, follicular, ovulatory), used very small subject populations, and collected very limited pharmacodynamic data. An example of a possible effect would be an increase in gastric emptying, which has previously been associated with the ovulatory phase, resulting in an increase in the rate of oral drug absorption. This would result in an increase in the peak plasma concentration and a decrease in the time to peak concentration with a concomitant increase in dynamic response or a decrease in the time to response.

Caffeine (oral) is commonly used as a stimulant to alleviate the effects of sleep deprivation. It is almost completely (99%) metabolized in the liver and therefore classified as a **low clearance, flow independent** drug. This means that its rate of inactivation is unaffected by delivery to the liver and can only be modified by a change in hepatic enzyme activity (7,8,18). However, at the present time there is no information on the effects of the menstrual cycle on enzyme activity (e.g. P-450).

Atropine, on the other hand is intramuscularly administered into the quadriceps. It is a **high clearance, flow dependent** drug whose absorption is dependent on muscle blood flow as opposed to gastric emptying like caffeine and triazolam (12). Atropine is currently fielded by the U.S. military for intramuscular administration upon exposure to nerve agents (organophosphates). Previous research by Kamimori et. al. (11) has demonstrated that physiological stress (mild exercise) significantly modified the kinetics of intramuscular atropine in young men. As a result the potential for a modification in atropine kinetics during different phases of the menstrual cycle is also a possibility.

Triazolam is a fast acting hypnotic, which is rapidly removed from the body and a leading candidate for fielding by the U.S. military. In contrast to caffeine it is completely and rapidly removed by the liver and is classified as **high clearance** and **flow dependent**. This means that its rate of removal is primarily dependent on its rate of delivery to the liver by the blood as opposed to enzyme activity. A change in the rate of gastric emptying has the potential to modify the absorption rate of the drug and concomitantly the onset of its dynamic responses. In addition, any change in hepatic blood flow would also result in a modification in triazolam clearance.

Cardio-green (ICG) is a tricarbocyanine dye and is classified as a **high clearance, flow dependent** drug (12). It is rapidly removed from the systemic circulation by liver cells and secreted into the bile. ICG is an inactive dye that is intravenously administered and can be used to indirectly quantify hepatic blood flow in humans (19,20).

The proposed study will provide information on the effects of the time of the menstrual cycle (luteal, ovulatory, & follicular): (A) on the pharmacokinetics of three drugs which are leading candidates for fielding (caffeine, triazolam) or are currently fielded by the U.S. military (atropine) and an inactive intravenous marker (cardio-green); (B) on hepatic blood flow (cardio-green) and drug metabolism (caffeine); and (C) in combination with a stimulant (caffeine), a depressant (triazolam), and a chemical defense treatment (atropine) on a variety of pharmacodynamic responses.

The purpose of this study was to determine:

1. The effects of the time of the menstrual cycle (luteal, ovulatory, & follicular) on the pharmacokinetics of three drugs which are leading candidates for fielding (caffeine, triazolam) or are currently fielded by the U.S. military (atropine) and an inactive intravenous marker (cardio-green).

2. The effect of the menstrual cycle on hepatic blood flow (cardio-green) and drug metabolism (caffeine).

3. The effect of the menstrual cycle in combination with a stimulant (caffeine), a depressant (triazolam), and a chemical defense treatment (atropine) on a variety of pharmacodynamic (Hormonal, physiological, performance, etc.) responses.

Methods

Subjects

The subject population consisted of twelve healthy, young (18-35 yrs), non-smoking women who were not or had not been using oral contraceptives for a minimum of three months prior to the study. Each volunteer passed a complete physical, completed a test of maximal aerobic capacity, was trained on the computerized Performance Assessment Battery (PAB), and recorded their daily basal body temperature prior to and during the study. Subjects also received a serum pregnancy test each month to verify that they were not pregnant. Each subject completed three tests with each of four different drugs in nine separate test trials over a three-month period (three trials per month). Each drug was administered during a complete menstrual cycle (about 28-30 days) during the follicular (2-6 days post menses), ovulatory (12-16 days post), and luteal (22-26 days post) phases. Cardio-green and halcion were administered on the same day as they both have a short half-life that would not interfere with each other as they use different elimination pathways. Drug order was counter balanced to avoid an order effect. One subject was dropped from the study due to scheduling problems. Characteristics of the subjects are presented in Table 1.

1. Test Procedure.

On each study day subjects reported to the lab at 0700 hrs in a post absorptive state having abstained from any alcohol, caffeine product, or pharmacologic agent during the previous 24 hrs. In addition, subjects abstained from any major physical activity for 12 hrs prior to reporting to the lab. A catheter was placed in an antecubital vein and patency was maintained with a normal saline drip. Subjects completed two additional practice trials (e.g. PAB) prior to the

collection of control data (blood, physiological, etc.). At approximately 0730 (time 0) subjects received the appropriate drug (300 mg oral caffeine, 0.25 mg oral halcion, 2.0 mg atropine sulfate (intramuscular) or cardio-green (0.5 mg/kg body weight, intravenous). Subjects maintained a semi reclining position in a hospital bed for 12 hrs following the administration of caffeine and atropine and for ten hrs following triazolam administration. Serial venous blood samples were collected intermittently from the catheter for 12 hrs. These samples were appropriately treated, separated, and analyzed or stored for later analysis. In addition, subjects reported to a designated clinic/lab for the collection of a 24 hr blood sample. Outlines of sample collections for each trial are included in Appendix C.

2. Blood Samples.

Blood analyses included the concentration of the drug, hormones (e.g. estrogen, progesterone, etc), and catecholamines. Portions of each blood sample were immediately analyzed for venous glucose, hemoglobin, hematocrit, and plasma protein levels. Glucose was determined with a glucose analyzer (Yellow Springs). Catecholamines were separated with alumina extraction and assayed by HPLC with electro chemical detection. Hormonal assays (e.g. cortisol, estrogen, etc.) were accomplished by spectroscopy and RIA through contract sources. Drug concentrations were determined by appropriate methods in our collaborators labs (caffeine, triazolam, atropine).

3. Caffeine Analytical Method:

The serum concentration of caffeine was determined by high performance liquid chromatography (HPLC) using a previously described method (21) with the following modifications. The mobile phase was modified to 1.75 mM H3PO4-acetonitrile-tetracydrofuran (98:1:1), a Nova-Pak column (Waters Millipore, Milford, MA) was substituted for the Supelco column, the injection volume was doubled to 30 ul and the flow rate was reduced to 0.6 ml/min. The HPLC system (Waters Millipore, Milford, MA) consisted of the following: an auto injector (model WISP 712), pump (model 510), a column heater (30° C) and a multiwave length detector (model 481) set at 273 nm. Assay sensitivity was 10 ng/ml with a within-day variation of less than 1 % and a between-day variation of less than 3%.

4. Triazolam Analytical Method:

Triazolam concentrations were quantified using electron-capture gas chromatographic analysis as described by Greenblatt et al. (22).

Table 1: Subject Characteristics

Subject #	Age (yrs)	Height (cm)	Weight (kg)	VO_{2max} (pre) (ml/kg/min)	VO_{2max} (post) (ml/kg/min)
01	25	160	56.8	48.8	46.1
02	22	162.5	59.1	34.6	36.5
03	26	167.6	61.4	44.4	42.0
04	30	162.5	59.1	43.7	36.9
05	29	167.6	63.6	39.2	37.6
06	26	170.2	54.5	30.4	28.6
07	19	165.1	67.3	27.6	
08	19	154.9	47.7	40.4	
09	20	172.7	61.4	36.1	
12	20	165.1	56.8	37.1	28.2
13	23	154.9	56.8	21.9	22.2
Mean	**23.54**	**163.9**	**58.6**	**36.7**	
STD	**3.93**	**5.73**	**5.1**	**7.9**	

5. Pharmacokinetic Data Analysis

Compartmental modeling was used to describe the pharmacokinetic parameters for caffeine after single dose administration to sleep deprived subjects. The following parameters were estimated for caffeine: Ka (absorption rate constant), lz (terminal elimination rate constant) and Vd/F (volume of distribution). The pharmacokinetic parameters were estimated utilizing the non-linear, least squares regression analysis program, WINNONLIN modeling program. Various weighting schemes were used to fit the data (e.g., 1, 1/y, 1/y2, y = caffeine serum concentration). The inverse assay variance was also used to weight the data. The AUC from time 0 to the last concentration time point ($AUC_{0-Cplast}$) was determined by the trapezoidal method.

The AUC_{0-E} was determined by the following equation:

$$AUC_{0-E} = AUC_{0-Cplast} + \frac{Cplast}{lz} \quad (1)$$

The oral Cl/F (clearance), $t1/2_{lz}$ (half-life), Cmax (maximum concentration) and Tmax (time of maximum concentration) were calculated in the usual manner. The choice of the appropriate pharmacokinetic model was based on standard goodness of fit criterion. "Goodness of fit" criteria was based on the final sum of squares, the weighted sum of squares, the comparison between observed and predicted concentration and effect levels, the coefficient of determination, the coefficient of variation associated with each parameter and the pattern of residuals. A parametric general linear model was applied to each of the above defined pharmacokinetic parameters. Statistical analysis employed a two-way ANOVA procedure from the SYSTAT statistical software. The analysis of variance model included the following factors: sequence, subject within sequence, period and treatment. Significance was achieved at the 95% confidence level ($p<0.05$).

6. Physiological Measures

Heart rate was monitored on-line with a Sensormedics EKG unit, and blood pressure was manually measured with a sphygmomanometer. The cardiac double product (CDP) was calculated as the product of heart rate and systolic blood pressure divided by 100.

7. Cognitive Performance, Mood, & Subjective Measures

The computerized Performance Assessment Battery (PAB) was used to evaluate cognitive performance. The PAB is a set of tests designed to measure changes in a number of simple and complex cognitive areas (23). The tasks used in this study include ten choice reaction time, logical reasoning, the stroop test, manikin, and serial addition/subtraction. Accuracy (percent correct responses), speed (responses/min), and throughput (accuracy * speed/100) were determined for each task.

Mood was assessed through a computerized version of the Profile of Mood States (POMS) that was incorporated into the PAB (24). Mood was subdivided into six subscales: tension, depression, anger, vigor, fatigue, and confusion.

Subjective measures of sleepiness (0-7 point scale) and headache (0-4) were also administered in conjunction with the PAB. Additional information on the PAB tasks, POMS, sleepiness and headache scales may be found in Appendix B.

Results and Discussion

Caffeine

1. Pharmacokinetics:

The sample population was reduced to ten subjects due to incomplete data for one of the participants. Fig 1 illustrates the mean caffeine plasma concentration versus time profiles for subjects in the luteal, follicular and ovulatory phases of the menstrual cycle. Mean (+ SEM) concentrations are presented in Table 5 (Appendix D). The pharmacokinetic disposition of caffeine in plasma followed a one compartment model. The estimated pharmacokinetic parameters are summarized in Table 2. The peak concentration (Cmax) of caffeine in plasma was found to be similar among the different phases; Cmax (follicular) = 7.29 ug/ml, Cmax (ovulatory) = 7.51 ug/ml and Cmax (luteal) = 7.13 ug/ml. However, the extent of absorption, as indexed by the area under the plasma concentration versus time curve (AUC), was higher in the ovulatory phase (108.3 ug/ml hr-1) as compared to the follicular (83.2 ug/ml hr-1) and the luteal (89.6 ug/ml hr-1). Due to the high intersubject variability, statistical significance was not achieved but the trend is noteworthy.

Superimposition of the luteal and follicular curves suggests similar absorption and elimination characteristics. Absorption appears to be very rapid as indicated by the time to reach peak caffeine plasma concentration (Tmax; follicular

= 1.75 hr and luteal = 1.78 hr) and the absorption rate constant (ka; follicular =1.78 hr-1 and luteal = 2.22 hr-1). The rate of absorption is highest in the ovulatory phase (ka = 2.99 hr-1) although it was not statistically significant. A concomitant reduction in caffeine elimination was also observed in the ovulatory phase as evidenced by a decrease in elimination rate (0.094 hr-1) and this trend was also apparent in the slower clearance seen in the ovulatory phase (3.371 l/hr) as compared to the clearance in the follicular phase (4.11 L/hr) and the luteal phase (3.63 L/hr). However, higher absorption and decreased elimination did not result in increased plasma concentrations.

Discussion

The trend toward a higher rate and extent of absorption in the ovulatory phase versus the luteal phase may be due to the influence of hormonal variation during the menstrual cycle on gastric emptying time. It has been shown that gastrointestinal transit time is significantly prolonged in the luteal phase (25) and appears to be related to high progesterone levels. However, only the follicular and luteal phases were studied (25) and no experiments were conducted to study the effect of the surge of luteinizing hormone (LH) which occurs immediately prior to ovulation. Failure to distinguish between the ovulatory and luteal phases may have prevented accurate reporting of the phase-related differences.

The slowed caffeine elimination in the luteal phase is consistent with the results generated from a previous study (26). However, the slowest elimination is found in the ovulatory phase suggesting that the sharp decrease in estrogen or the peak levels of LH may be responsible for the observed fluctuations. These variations may also affect hepatic metabolism, thereby influencing elimination.

Contradictory results from studies focusing on the menstrual cycle related changes in drug pharmacokinetics may be due to high intersubject variability and a relatively small sample sizes. Nevertheless, it is apparent that phase-related changes in caffeine pharmacokinetics need to be investigated more closely. The changes seen in the current study do not have significant clinical implications in terms of dosage adjustment. However, dose-dependent caffeine pharmacokinetics has been reported in sleep deprived individuals and may necessitate studies examining the effect of the menstrual cycle in a representative population (13).

FIG. 1 MEAN PLASMA CAFFEINE CONCENTRATION DURING 3 PHASES OF THE MENSTRUAL CYCLE FOLLOWING A 300 mg ORAL DOSE

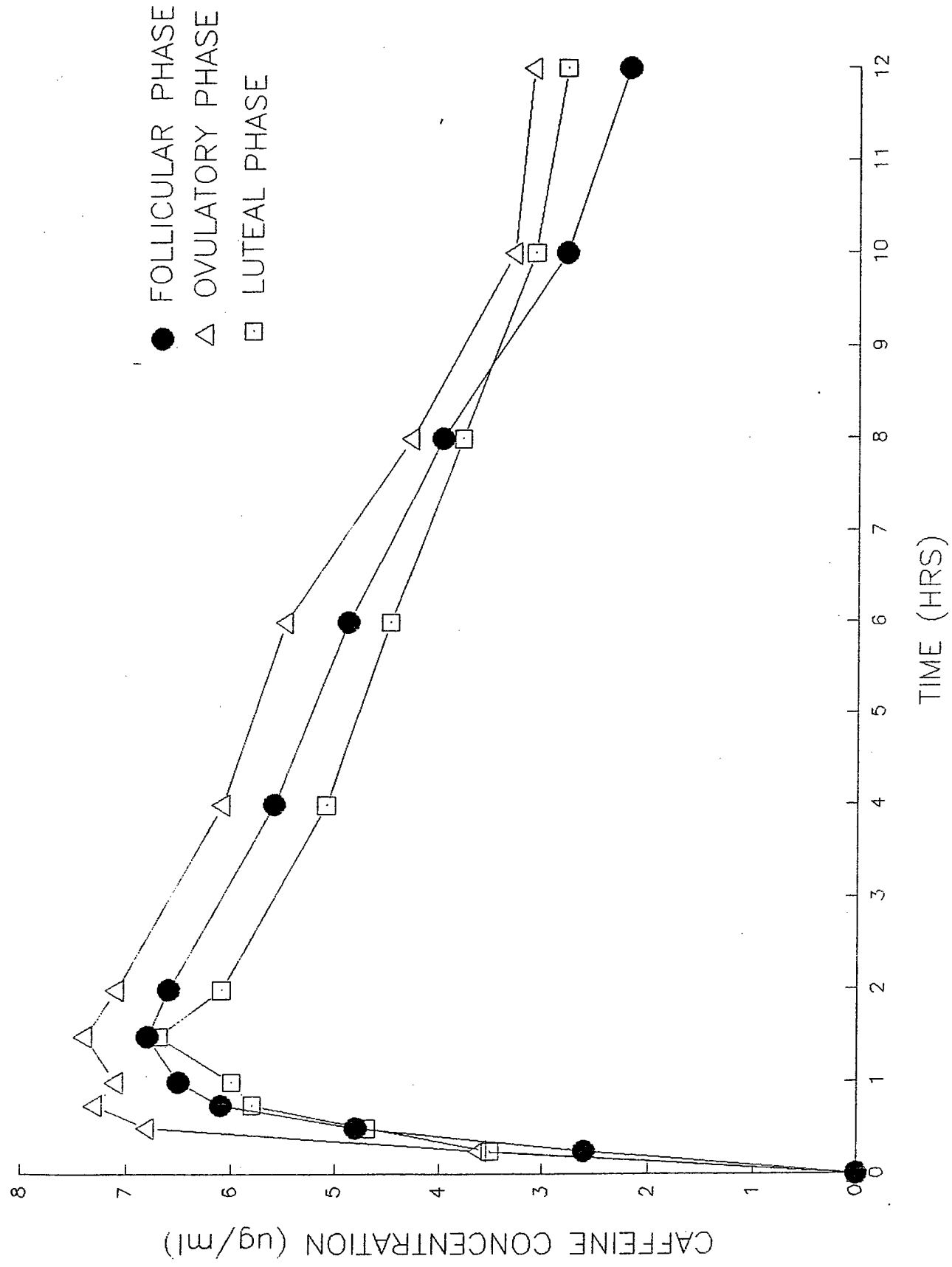


Table 2: Pharmacokinetic Parameters - Caffeine

		Cmax (ng/ml)	Tmax (hr)	AUC (ng/ml*hr$^{-1)}$	k 01	k 10	t ½ (hr)	CL (l)
FOL	X	7.3	1.7	83.2	1.8	0.115	5.8	4.1
	SEM	0.5	0.1	10.1	0.2	0.01	0.4	0.1
OVU	X	7.5	1.5	108.3	3.0	0.094	7.7	3.4
	SEM	0.6	0.2	17.2	0.6	0.04	1.0	0.1
LUT	X	7.1	1.8	89.6	2.2	0.101	6.9	3.6
	SEM	0.5	0.3	9.4	0.4	0.03	0.6	0.1

2. Hormonal Data:

Plasma aldosterone and catecholamine and aldosterone analysis has been completed and the concentration data is included in Tables 6 & 7 (Appendix D). There were no significant differences between menstrual cycle phases.

3. Physiological Variables:

As illustrated in Fig 2, the cardiac double product (CDP) was not significantly affected by either 300 mg of oral caffeine or menstrual cycle phase. Heart rate, blood pressure, and CDP data are presented in Tables 8 & 9 (Appendix D).

4. Hematological Parameters:

Plasma glucose, free fatty acid, hematocrit, hemoglobin, plasma protein, plasma volume, sodium, potassium, and osmolality, data are presented in Tables 10-13 (Appendix D). Additional analyses have not been completed due to funding constraints.

5. Cognitive Performance, Mood, & Subjective Measures:

Accuracy, speed, and throughput (Mean + SEM) for each of the five cognitive tasks are presented in Tables 14-18 (Appendix D). Subjective sleepiness data are presented in Table 19 and POMS data in Tables 20-21 (Appendix D). Menstrual cycle phase had no significant effect on performance of these cognitive tasks.

Atropine

1. Pharmacokinetics:

At the present time serum atropine concentrations have not been accomplished. The previously available antibody for this assay is no longer available. A mass spectrometer methodology was investigated however funding has not been available to pursue this assay.

2. Hormonal Data:

Plasma aldosterone and catecholamine analysis has been completed and the concentration data is included in Tables 22 & 23 (Appendix D). There was no significant difference due to menstrual cycle phase.

3. Physiological Variables:

As illustrated in Fig. 3A, 2.0 mg of intramuscular atropine resulted in a significant increase in heart rate which persisted for three hrs. There was no significant difference between menstrual phases. Systolic blood pressure did not appear to be significantly affected by atropine and there was no significant difference between menstrual phases (Fig. 3B). Fig. 4 represents the effects of atropine on the cardiac double product. The CDP was significantly increased in all three groups for two hrs following the administration of atropine but there was no difference between phases. Heart Rate and CDP data (Table 24) and blood pressure data (Table 25) can be found in Appendix D.

4. Hematological Parameters:

Plasma glucose, free fatty acid, hematocrit, hemoglobin, plasma protein, plasma volume, sodium, potassium, and osmolality, data are presented in Tables 26-29 (Appendix D). No additional analyses were completed due to lack of funding.

5. Cognitive Performance, Mood, & Subjective Measures:

Accuracy, speed, and throughput (Mean + SEM) for each of the five cognitive tasks are presented in Tables 30-34 (Appendix D). Fig. 5 illustrates the effects of atropine on subjective sleepiness. There was no significant difference between phases, however there was an increase in sleepiness in all groups, which persisted throughout the twelve hr period. Subjective Sleepiness data are presented in Table 35 (Appendix D). There was a significant decrease in vigor (Fig. 6) and increase in fatigue (Fig. 7) for all phases following the administration of atropine. In addition, as illustrated in Fig. 8, confusion was also significantly increased during the first four hrs following atropine administration. POMS data are presented in Tables 36 & 37 (Appendix D).

As shown in Fig. 9 and Table 38 (Appendix D), the administration of 2.0 mg of intramuscular atropine all of the subjects reported headaches ranging from mild to debilitating ("1"-"4" on the headache scale, "0" = no headache). Onset of the headache occurred between two and six hrs following drug administration and duration varied from 6-8+ hrs.

Triazolam

1. Pharmacokinetics:

Non-compartmental analysis was used to estimate the pharmacokinetic parameters for triazolam and ICG. Figure 10 presents the triazolam plasma concentrations vs time profile for subjects enrolled in the study. Concentration data is

FIG. 2

CARDIAC DOUBLE PRODUCT FOLLOWING 300 mg ORAL CAFFEINE DURING 3 PHASES OF THE MENSTRUAL CYCLE

presented in Table 39 (Appendix D). The pharmacokinetic parameters for triazolam are presented in Table 3. No significant differences ($p < 0.05$) were found for any of the model-independent parameters estimated. The Cmax was found to be highest in the follicular phase (2.05 ng/ml) vs the ovulatory (1.78 ng/ml) and the luteal phase (1.92). The extent of absorption as evidenced by AUC was slightly higher in the luteal phase (9.20 ng/ml hr-1) as compared to the follicular (8.87 ng/ml hr-1) and the ovulatory (8.42 ng/ml hr-1) phase. The distribution pattern of triazolam appears to differ in the luteal phase. The distribution of triazolam in the luteal phase (Vd/F = 107 L) was much smaller as compared to the follicular (138 L) and the ovulatory phase (133 L). Even though these differences did not reach significance there is a definite trend toward a lower distribution in the luteal phase. In terms of triazolam elimination, the clearance is much higher in the follicular phase (54.6 L/hr) as compared to the ovulatory (33.8 L/hr) and luteal (32.3 L/hr). There is a major trend toward an increase in clearance during the follicular phase.

Discussion

The results indicate that menstrual cycle phase may have an effect on the pharmacokinetics of triazolam and ICG. The lack of statistical differences may be due to the number of subjects enrolled in the study. The trends observed for the pharmacokinetic parameters in both phases suggest that with additional subjects a significant change in parameters may have been observed. Gender-related discrepancies in drug pharmacokinetics have been observed for several therapeutic agents[1,2]. Gender-specific pharmacokinetic differences that exist in drug disposition may be due in part to hormone fluctuations from the menstrual cycle or from the administration of oral contraceptives. In general, women tend to have altered distribution of lipophilic drugs[19-22] and altered cytochrome P450-3A4 activity[23-27] as compared to men. Further, studies have suggested that the menstrual cycle may influence the absorption process by altering gastrointestinal transit time during the luteal phase.[3-7] Fluctuating levels of estrogen and progesterone during the menstrual cycle may play a significant role in the disposition of certain agents in women.

In this study, the hormone levels were determined on three separate occasions over a 28-day menstrual cycle. Hormonal levels were collected once during days 2-6 (representing levels in the follicular phase), days 13-16 (ovulatory phase) and days 22-26 (luteal phase). Triazolam and ICG were administered during the time of hormone sampling. Due to the retrospective nature of this study and the

FIG. 3A

HEART RATE FOLLOWING 2.0 mg INTRAMUSCULAR ATROPINE DURING 3 PHASES OF THE MENSTRUAL CYCLE

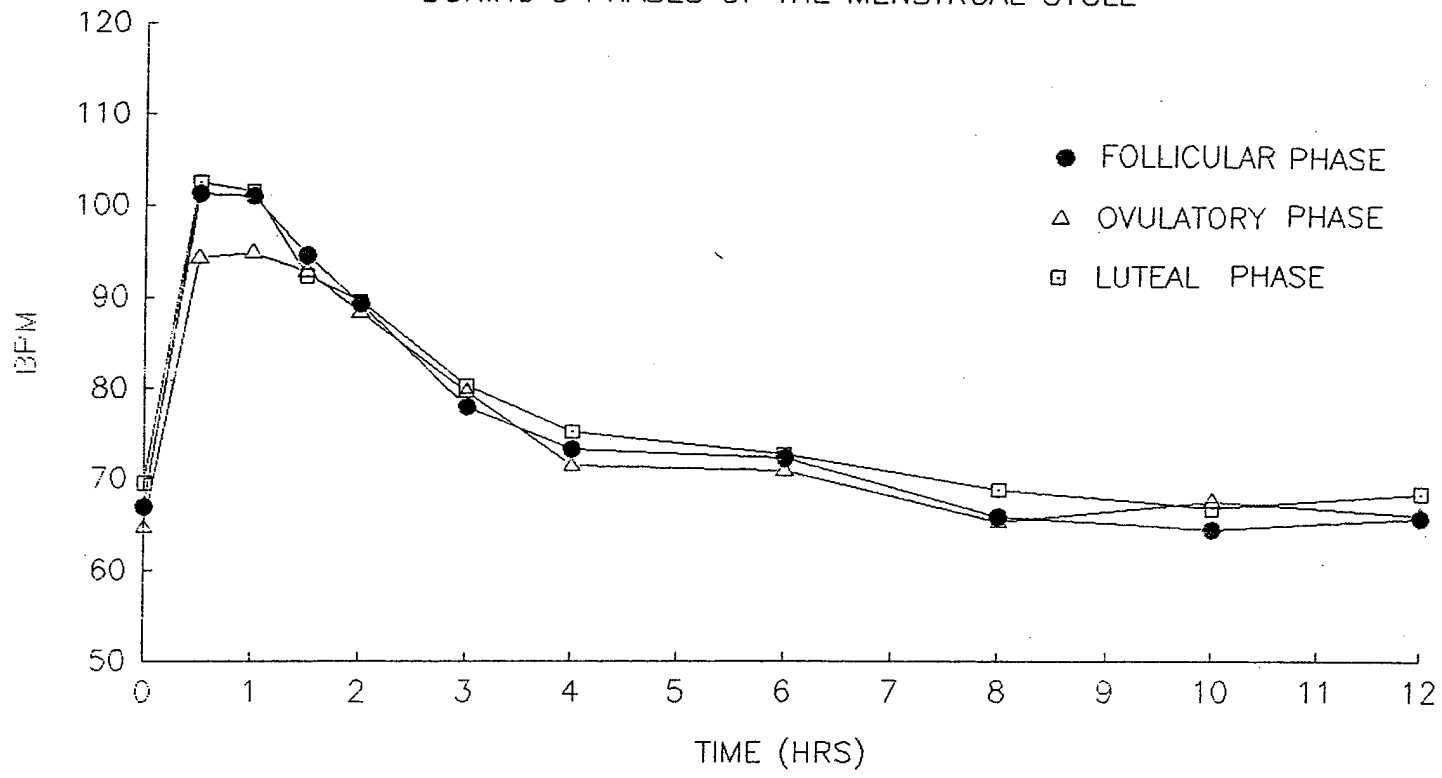


FIG. 3B

SYSTOLIC BLOOD PRESSURE FOLLOWING 2.0 mg INTRAMUSCULAR ATROPINE DURING 3 PHASES OF THE MENSTRUAL CYCLE

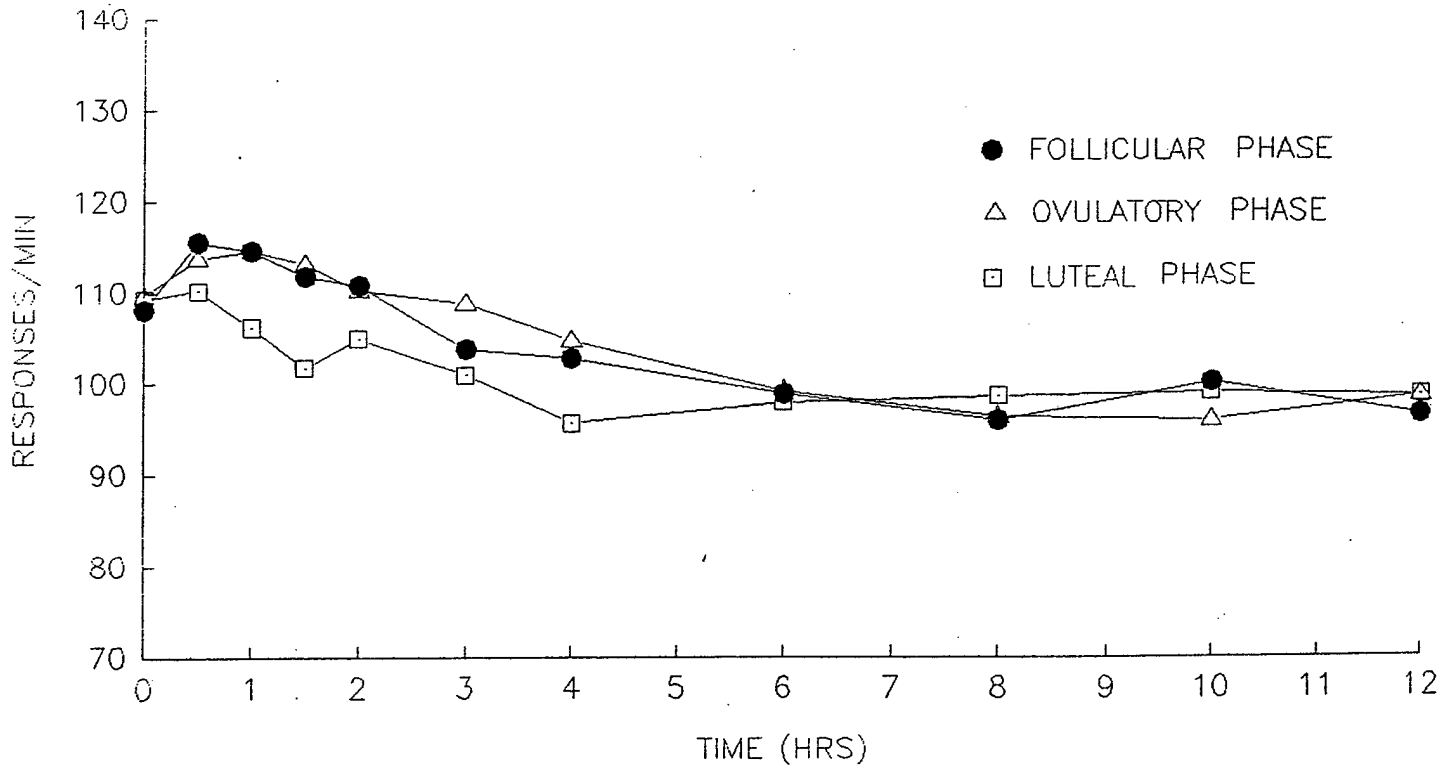


FIG. 4

CARDIAC DOUBLE PRODUCT FOLLOWING 2.0 mg INTRAMUSCULAR ATROPINE DURING 3 PHASES OF THE MENSTRUAL CYCLE

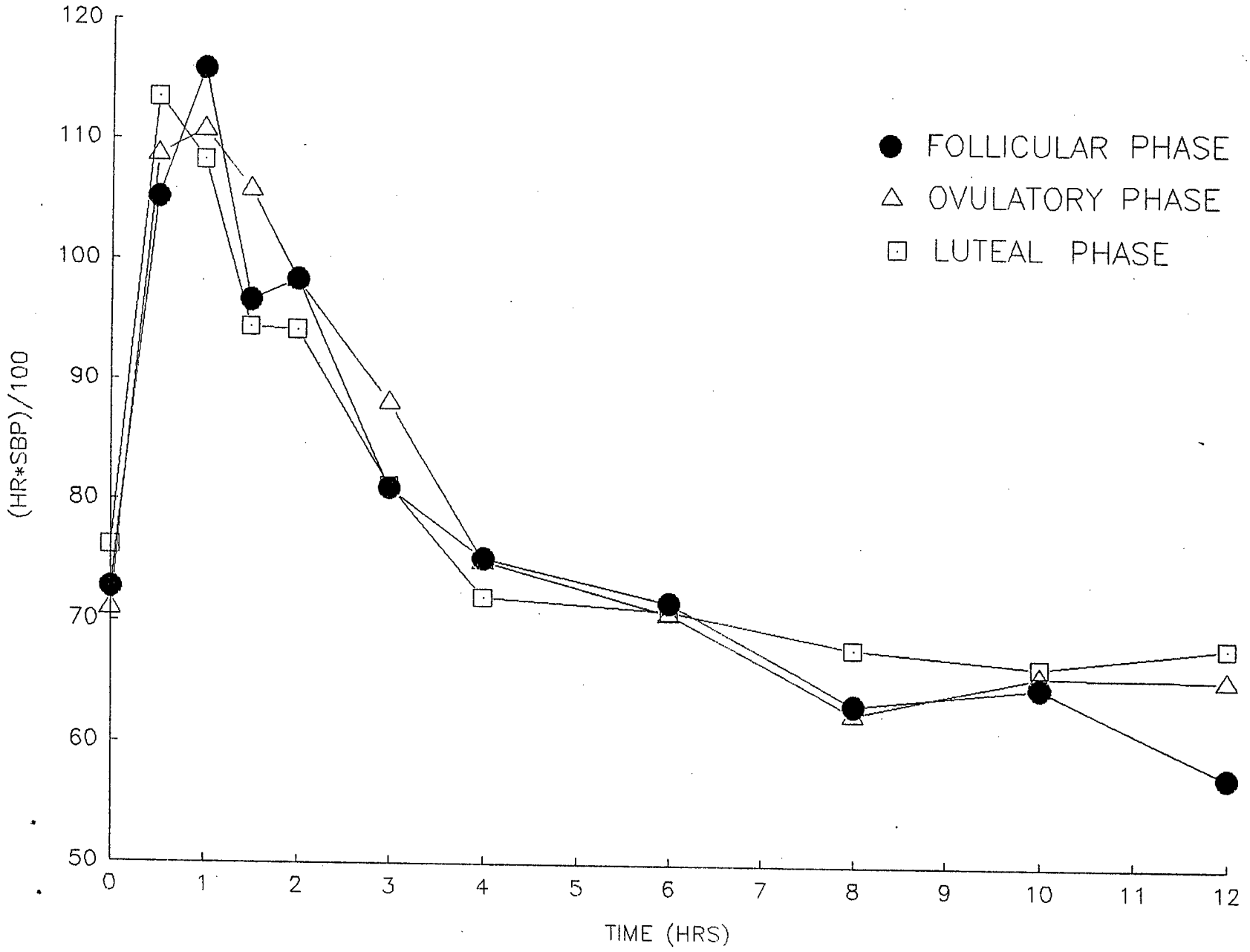


FIG. 5

SUBJECTIVE SLEEPINESS SCORE BY PHASE
FOLLOWING 2.0 mg INTRAMUSCULAR ATROPINE

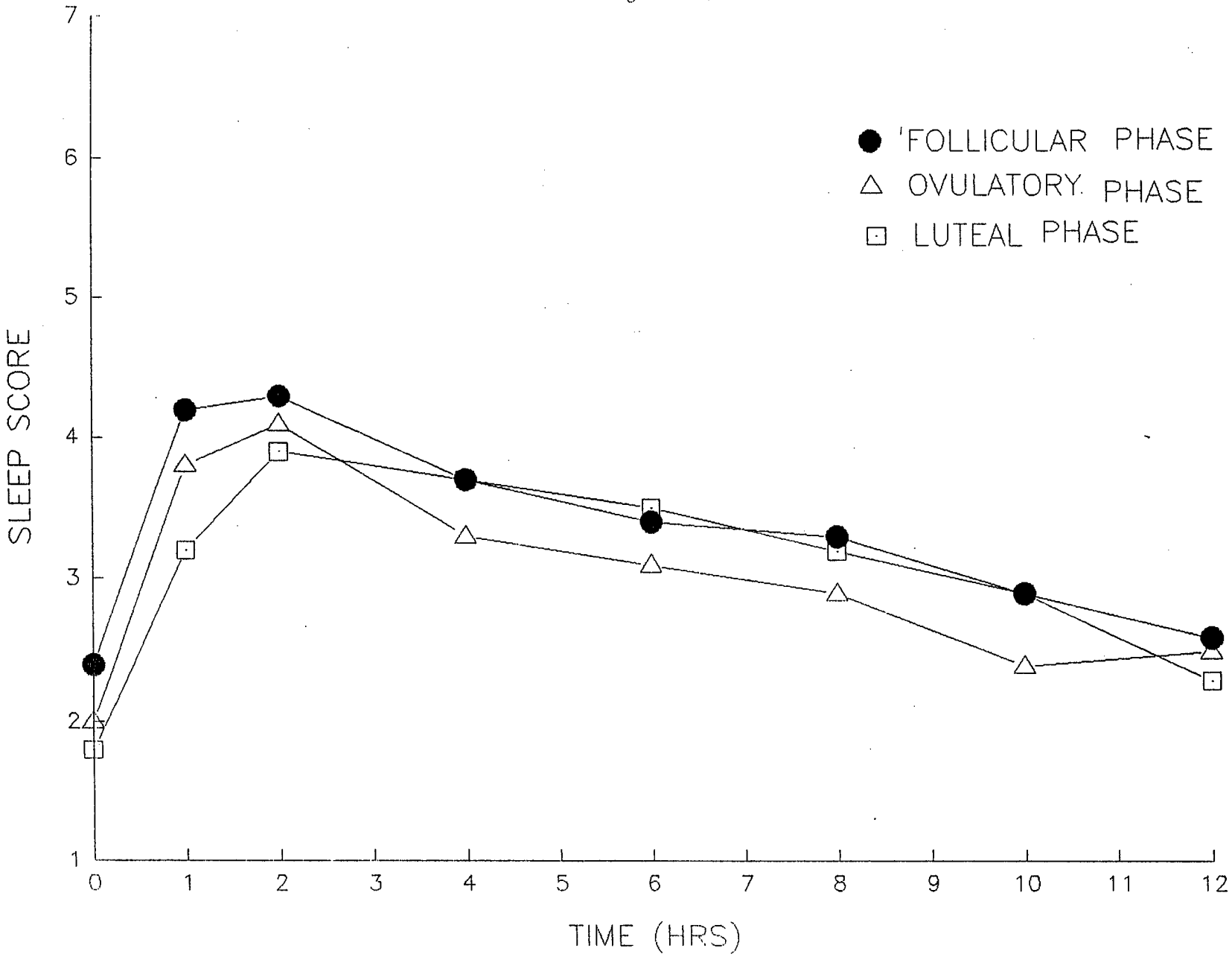


FIG. 6 VIGOR SCORE BY PHASE FOLLOWING 2.0 mg INTRAMUSCULAR ATROPINE

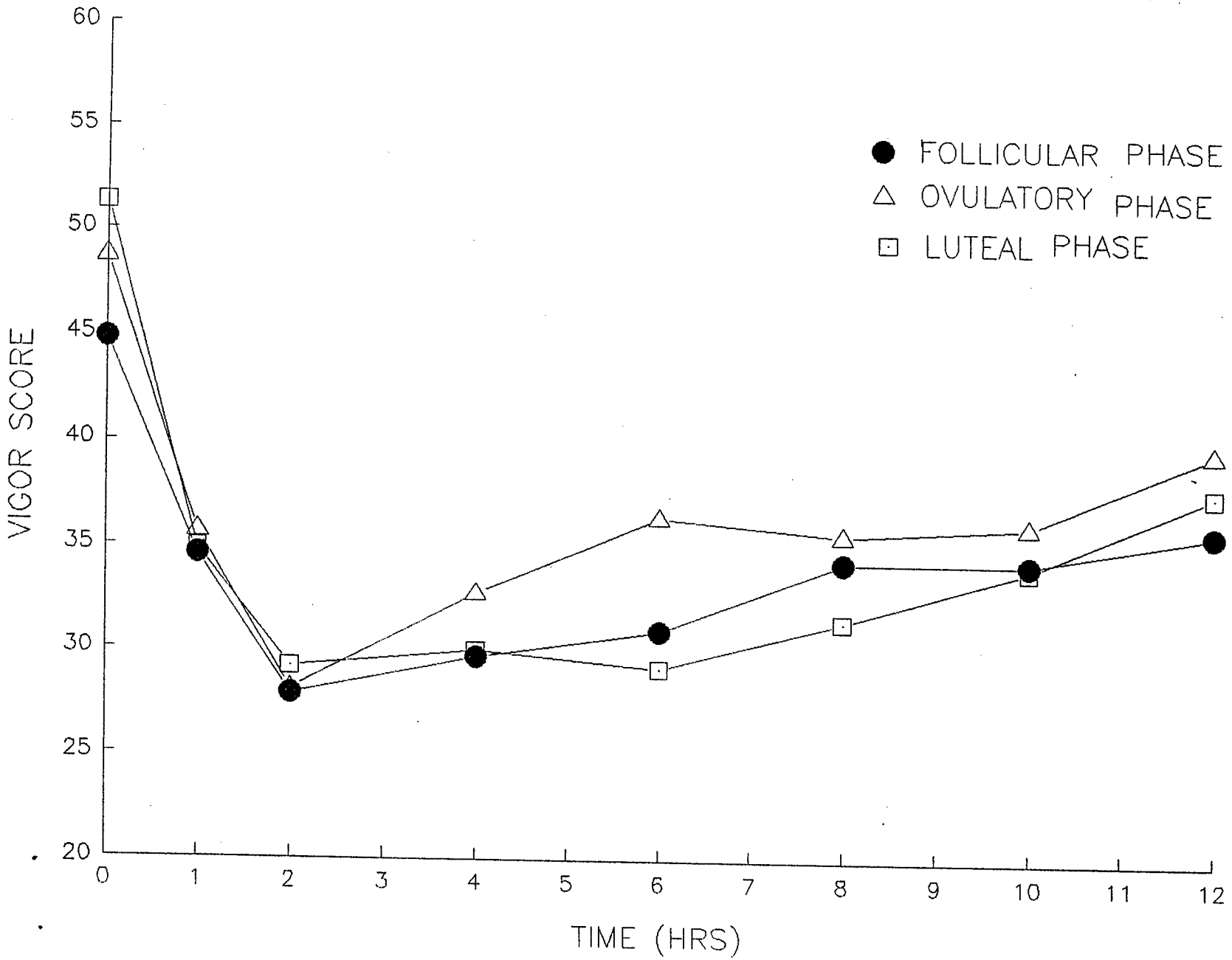
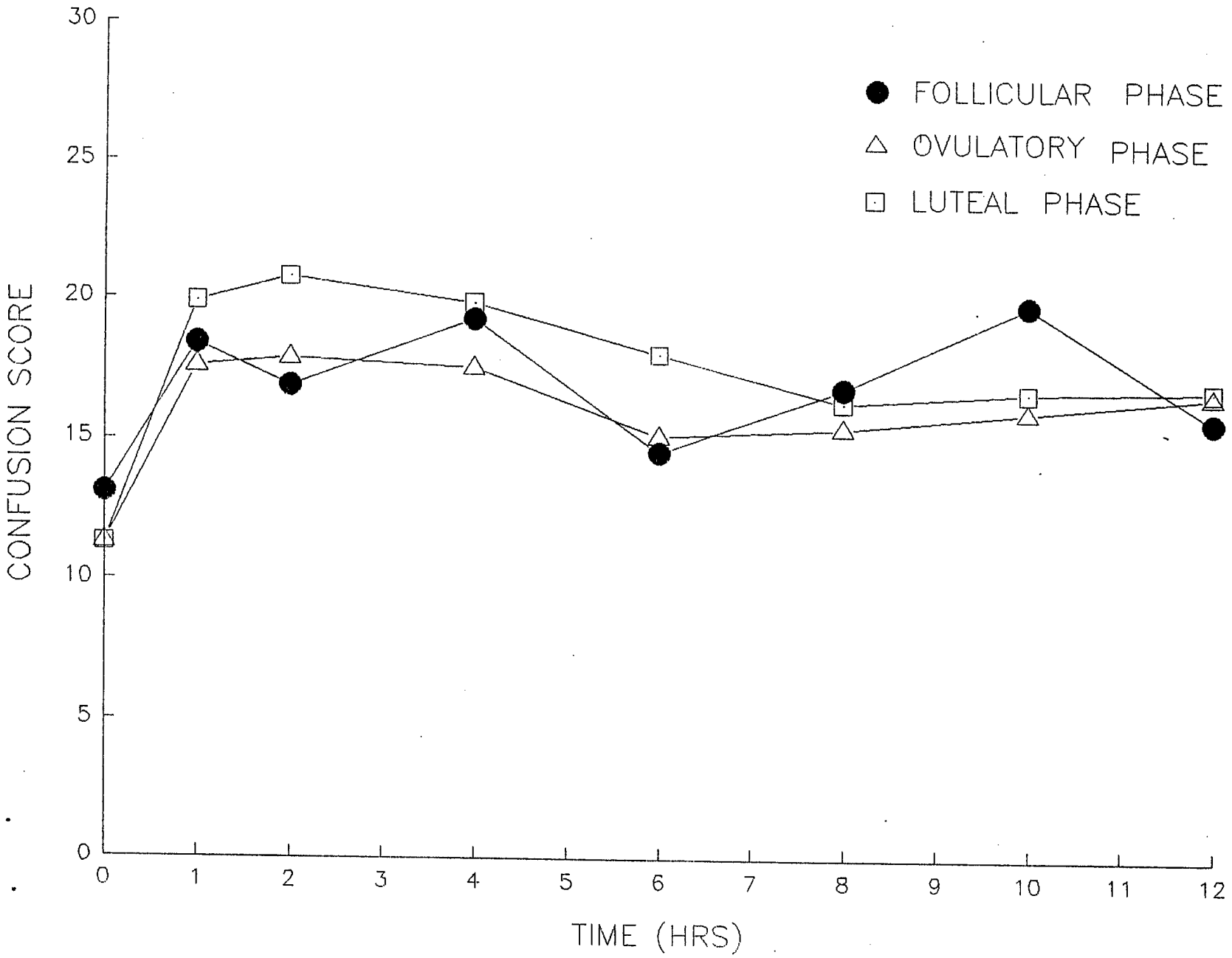


FIG. 7 FATIGUE SCORE BY PHASE FOLLOWING 2.0 mg INTRAMUSCULAR ATROPINE

FIG. 8 CONFUSION SCORE BY PHASE FOLLOWING 2.0 mg INTRAMUSCULAR ATROPINE



variability of a normal menstrual cycle, it is apparent that the dosing for all subjects may not have taken place on the same day of the cycle. Furthermore, since a two-day window was used for ovulation, it may have been missed in some subjects. It should be noted that all participants in the study, were previously determined to be normal healthy individuals with "normal" menstrual cycles.

In terms of gender related differences in the rate of triazolam absorption, our values (Table 2) for mean C_{max} (1.78 - 2.05 ng/ml) and mean T_{max} (1.03 - 1.23 hr) are consistent with previously reported parameters.[28, 29] A mean C_{max} of 1.94 ng/ml and a mean Tmax of 2.06 hr were found after a single oral dose of triazolam to normal healthy males.[28] In another investigation with male and female subjects, Greenblatt *et al.*[29] reported, mean parameter values of 2.56 ng/ml and 0.96 hr for C_{max} and T_{max}, respectively after triazolam administration. The extent of triazolam absorption (AUC_{inf}) in our study ranged from 8.42 - 9.2 ng/ml hr. Again these values were consistent with previously reported AUC_{inf} values of 9.22 ng/ml·hr[28] and 7.23 ng/ml· hr[29].

Table 2 also presents the elimination parameters for triazolam in the follicular, ovulatory and luteal phases. The oral clearance and half-life values were 538 - 565 ml/min and 2.97 - 3.30 hr, respectively in our eumenorrheic subjects. There appears to be no gender related differences in triazolam elimination, since previously reported values for oral clearance (571 and 576 ml/min) and elimination half-life (2.34 and 2.42 hr) are comparable.[28,29]

The objective of this study was to examine the influence of the menstrual cycle on the pharmacokinetics of triazolam in normal, healthy eumenorrheic females. Although, there were no statistically significant differences in the pharmacokinetics of triazolam, there were noticeable trends in certain parameters. The extent of absorption as indicated by AUC_{inf} was slightly higher in the luteal phase (9.20 ng/ml·hr) as compared to the follicular (8.87 ng/ml·hr) and the ovulatory (8.42 ng/ml·hr) phases. In addition, T_{max}, an indicator of the rate of drug absorption, was longest in the luteal phase (1.41 hr) as compared to the follicular (1.23 hr) and ovulatory (1.03 hr) phases. The trend of a higher AUC_{inf} and longer T_{max} in the luteal phase suggests an increase in the extent of absorption and a decrease in the rate of absorption in this phase. This trend may be due to a progesterone induced reduction in gastric emptying or a prolonged small intestinal transit time in the luteal phase which has been previously reported.[3-7]

Neither the distribution nor clearance of triazolam was

FIG. 9

SUBJECTIVE HEADACHE SCORE FOLLOWING 2.0 mg INTRAMUSCULAR ATROPINE

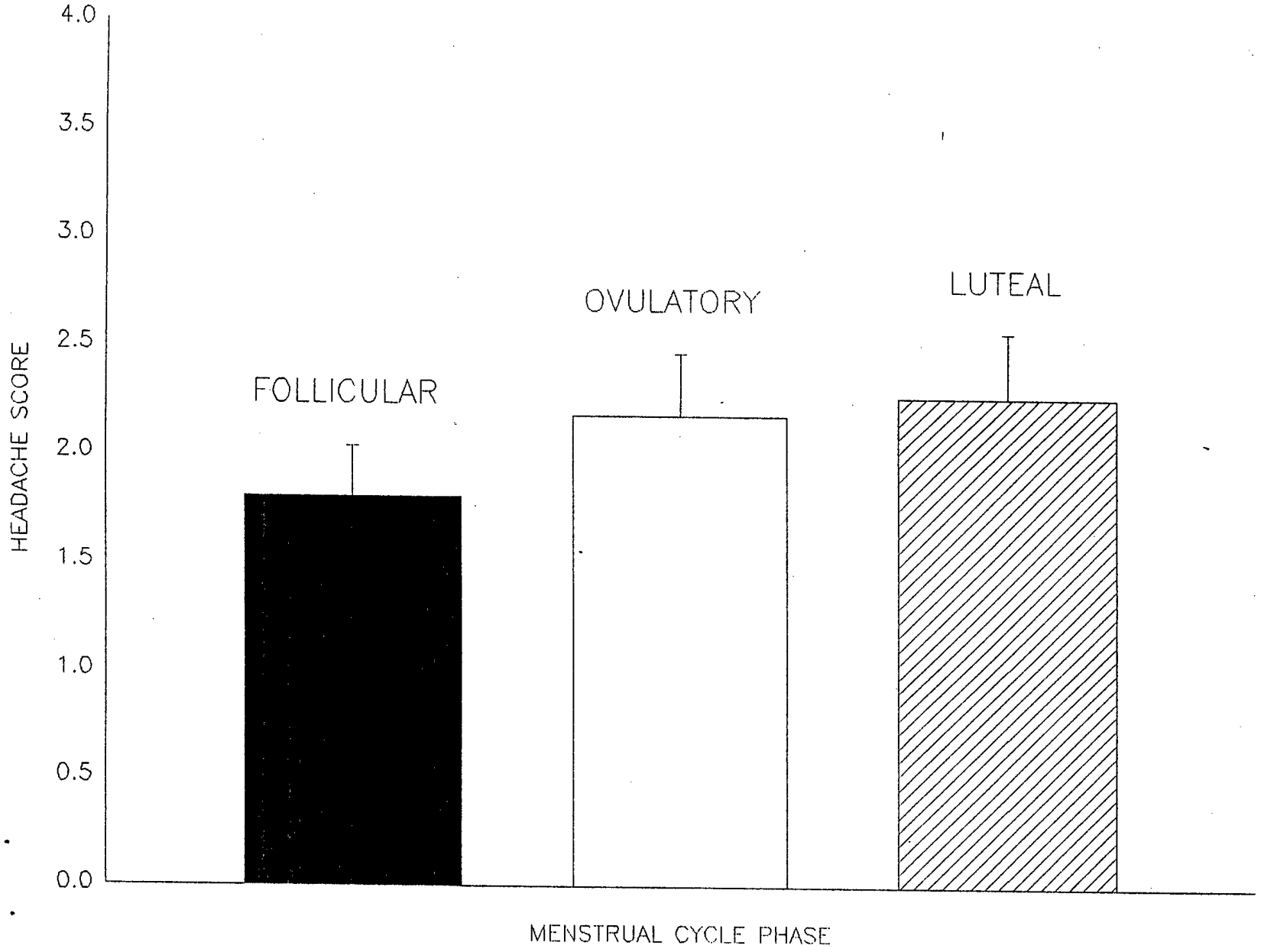


FIG. 10

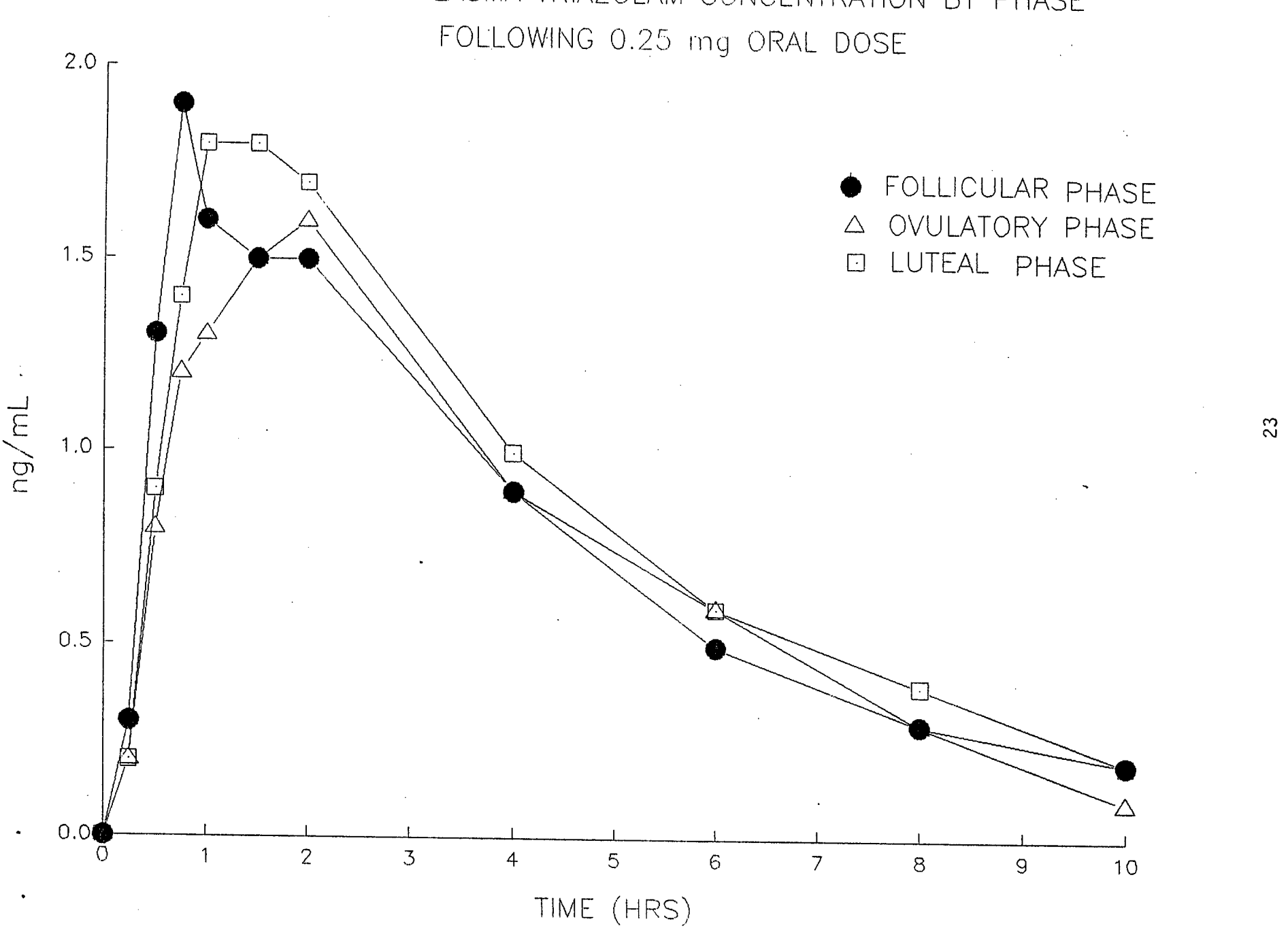

MEAN PLASMA TRIAZOLAM CONCENTRATION BY PHASE
FOLLOWING 0.25 mg ORAL DOSE
2.0
1.5
1.0
0.5
0.0
ng/mL
0
1
2
3
4
5
6
7
8
9
10
TIME (HRS)
FOLLICULAR PHASE
OVULATORY PHASE
LUTEAL PHASE

Table 3: Phamacokinetic Parameters - Triazolam

		Cmax (ng/ml)	Tmax (hr)	AUC (ng/ml*hr)	MRT (hr)	V/F (l)	Cl/F (l/hr)
FOL	X	2.1	1.2	8.9	4.8	138.1	54.9
	SEM	0.4	0.2	1.0	0.3	16.4	4.1
OVU	X	1.8	1.0	8.4	4.6	133.2	33.9
	SEM	0.2	0.2	0.9	0.4	16.7	4.1
LUT	X	1.9	1.4	9.2	4.3	107.2	32.3
	SEM	0.2	0.1	1.0	0.2	9.3	5.3

altered significantly across the menstrual cycle phases. The distribution pattern of triazolam appeared to differ in the luteal phase. The mean volume of distribution of triazolam in the luteal phase (107.2 L) was much smaller as compared to the follicular (138.1 L) and the ovulatory phase (133.2 L). Even though these differences did not reach significance there was a definite trend toward a lower distribution in the luteal phase. In terms of drug elimination, the clearance was comparable in the follicular phase (546 ml/min) as compared to the ovulatory (565 ml/min) and luteal phase (538 ml/min) phases.

2. Hormonal Data:

Plasma catecholamine and cortisol analysis has been completed and the concentration data is included in Tables 40 & 41 (Appendix D). Analysis of the data was not completed due to lack of funding.

3. Physiological Variables:

Heart rate and CDP data are presented in Table 42 (Appendix D). Blood pressure data is presented in Table 43 (Appendix D). There was no significant difference due to menstrual cycle phase.

4. Hematological Parameters:

Plasma glucose, hematocrit, hemoglobin, plasma protein, and plasma volume data are presented in Tables 44-46 (Appendix D). Additional analyses were not completed due to lack of funding.

5. Cognitive Performance, Mood, & Subjective Measures:

Fig. 11A illustrates the effects of 0.25 mg of oral triazolam on accuracy on the serial addition/subtraction task. There was a small but non-significant decrease in accuracy at 1.5 hr, with no difference between phases. However, there was a significant decrease in speed in all phases as seen in Fig. 11B. Once again there was no difference between phases. This translated into a significant decrease in throughput at 1.5 hr as shown in Fig. 12. As illustrated in Fig. 13, a similar decrease in performance was also observed in the choice reaction task, although this decrement appeared to persist through 3.0 hr post administration. Accuracy, speed, and throughput (Mean + SEM) for each of the five cognitive tasks are presented in Tables 47-51 (Appendix D).

As shown in Fig. 14, subjects reported an increase in subjective ratings of sleepiness 1.5 hr following administration of triazolam. There was no difference between

FIG. 11A

ACCURACY ON SERIAL ADDITION/SUBTRACTION TASK BY PHASE
FOLLOWING 0.25 mg ORAL DOSE OF TRIAZOLAM

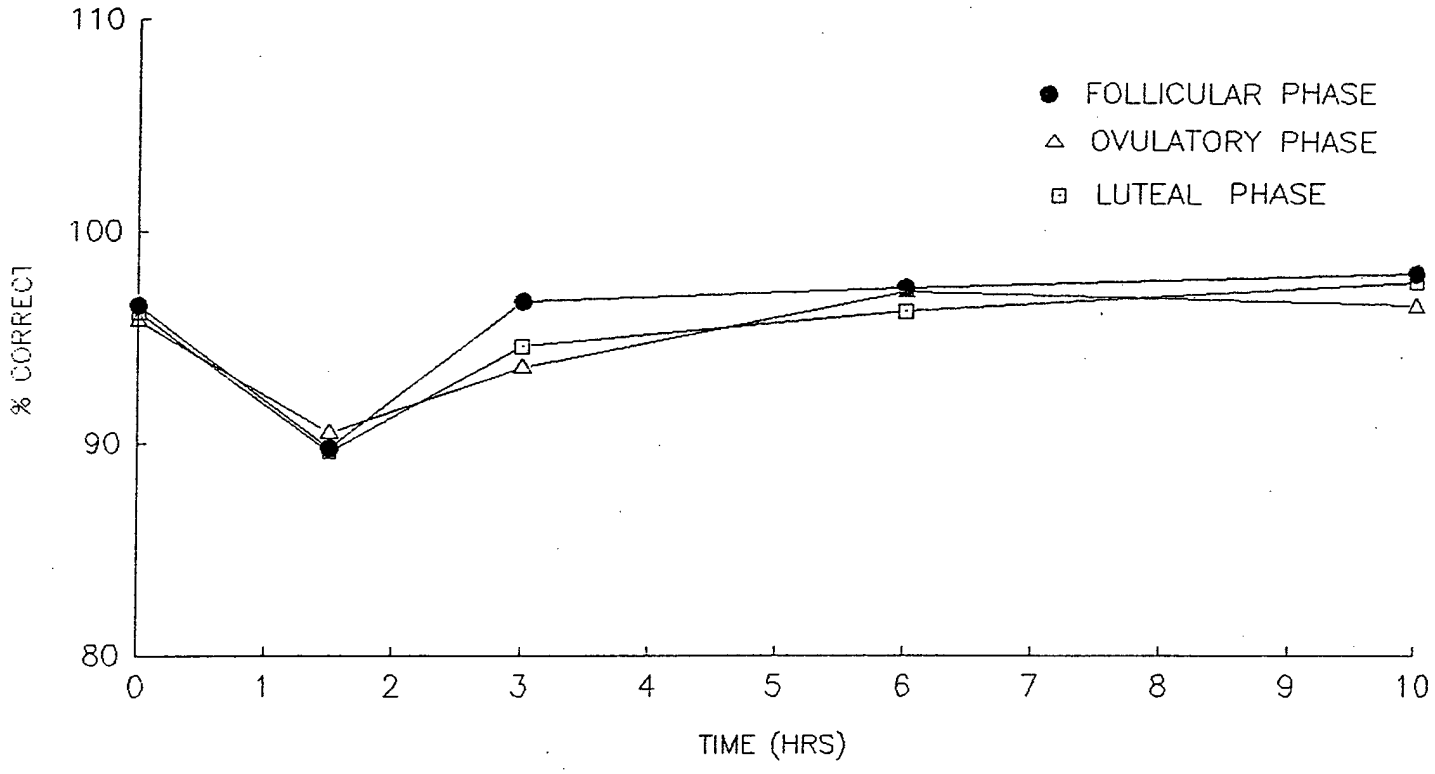


FIG. 11B

RESPONSE SPEED ON SERIAL ADDITION/SUBTRACTION TASK
BY PHASE FOLLOWING 0.25 ORAL DOSE OF TRIAZOLAM

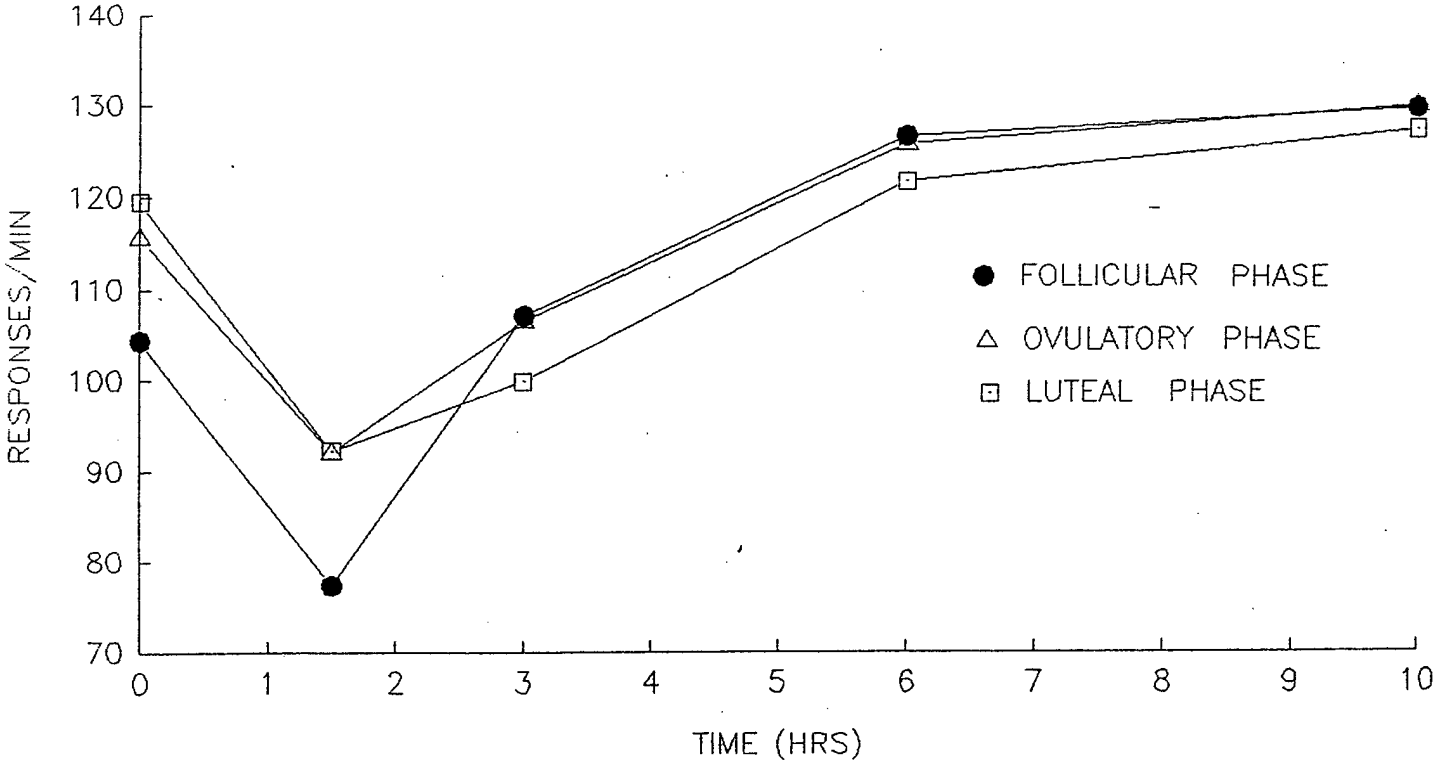


FIG. 12 THROUGHPUT ON SERIAL ADDITION/SUBTRACTION TASK BY PHASE FOLLOWING 0.25 mg ORAL DOSE OF TRIAZOLAM

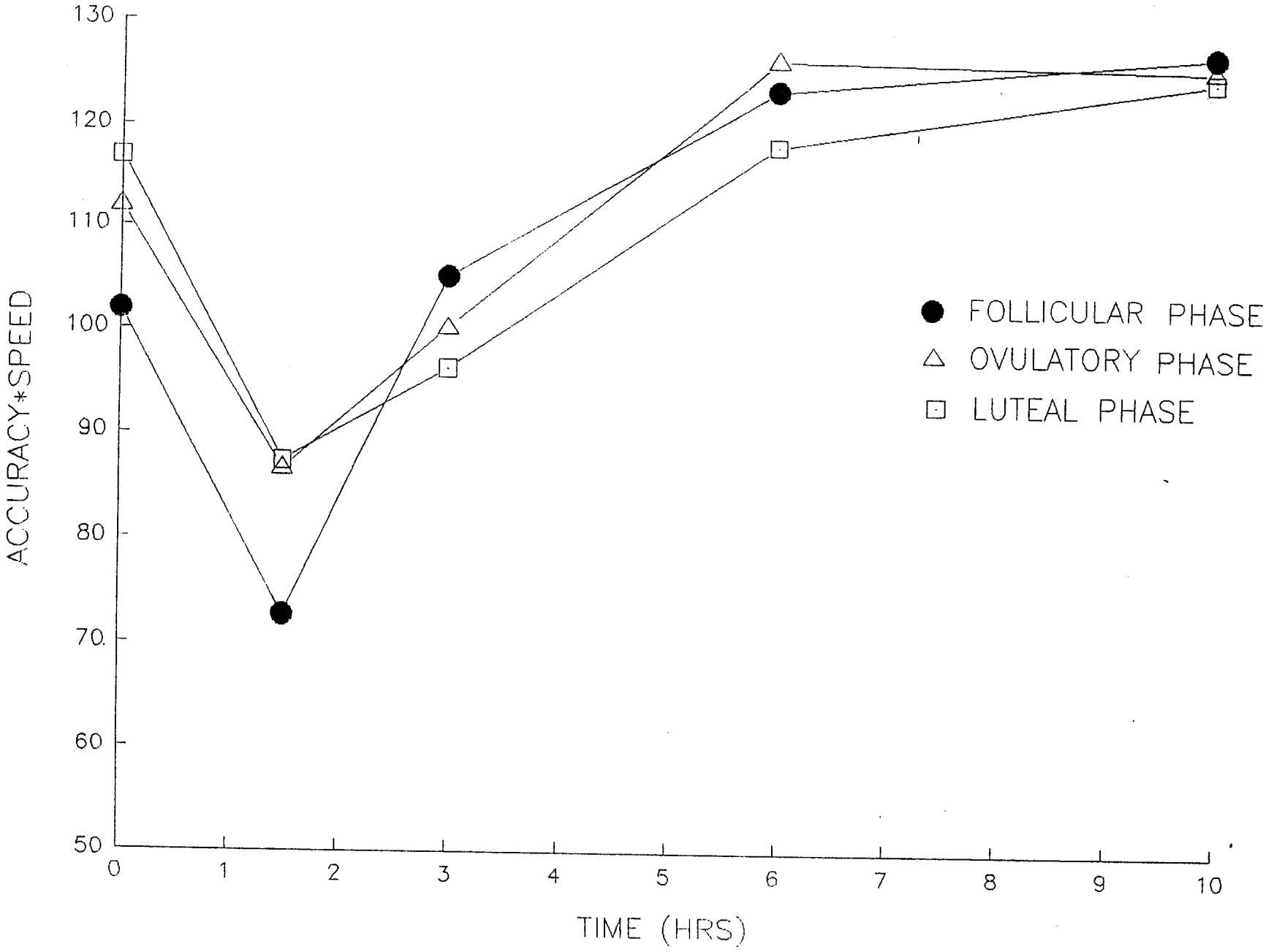
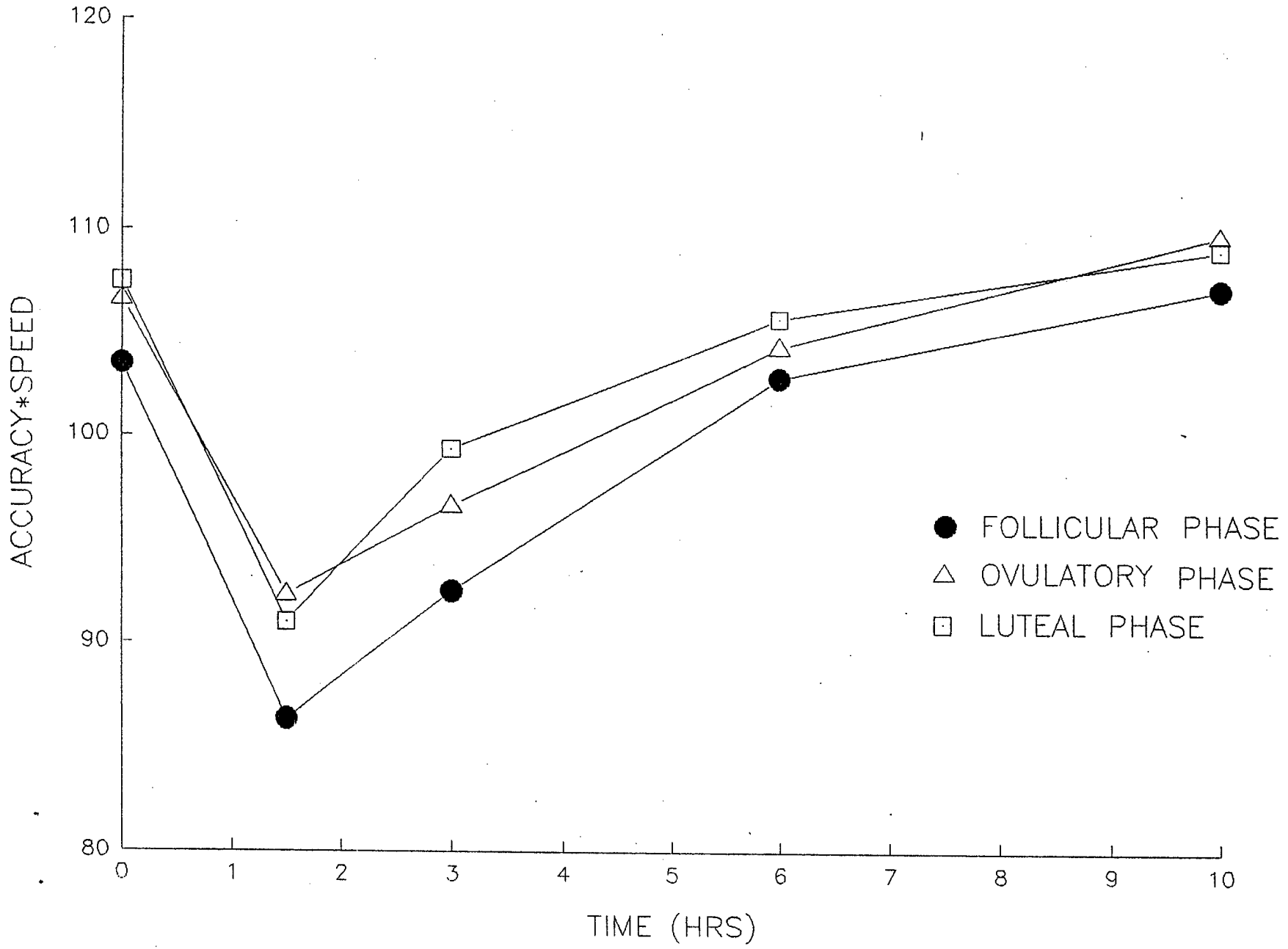


FIG. 13

THROUGHPUT ON CHOICE REACTION TASK BY PHASE
FOLLOWING 0.25 mg ORAL DOSE OF TRIAZOLAM



phases. The increase in sleepiness occurred in conjunction with the peak triazolam concentration and coincided with the decrease in cognitive performance.

There was no significant change in any subscale of the POMS following triazolam administration. POMS data are presented in Tables 53 & 54 (Appendix D).

Cardio-Green

1. Pharmacokinetics:

Indocyanine green, an indirect measure of liver blood flow, revealed no statistically significant differences in mean pharmacokinetic parameters (Table 3) after a single bolus dose during the follicular, ovulatory and luteal phases. The AUC_{inf} was much higher in the follicular phase (121.6 μg/ml·min) as compared to the ovulatory (78.7 μg/ml·min) and luteal phase (84.5 μg/ml·min). Associated with this, the clearance observed for the follicular phase (0.30 l/min) was lower as compared to the ovulatory (0.38 l/min) and luteal (0.36 l/min) phases. These results suggest that the liver blood flow is lowest during the follicular phase. Based on these results, a decrease in the clearance of a high extraction drug might be expected during the follicular phase of the menstrual cycle.

In conclusion, these results indicate that the phases of the menstrual cycle may have an effect on the pharmacokinetics of triazolam and indocyanine green. However, there were no statistically significance differences in pharmacokinetic parameters for either triazolam or ICG across the menstrual cycle phases. Lack of definitive results from menstrual cycle studies may be due to: (1) high intersubject variability, (2) relatively small sample sizes and (3) retrospective determination of hormone levels and hence phases in the subjects. Future study designs should include an assessment of hormone levels over multiple menstrual cycles to better identify phases. Nevertheless, it is apparent that phase-related trends in triazolam and ICG pharmacokinetics need to be investigated more closely.

REPORTABLE OUTCOMES:

Abstracts:

The Influence of the Menstrual Cycle on Triazolam and Indocyanine Green Pharmacokinetics. N. Sirisuth, G. Kamimori, D.J. Greenblatt, N.D. Eddington. Presented at the national meeting of the American Association of Pharmaceutical Scientists 1997

The Effect of Menstrual Cycle Phase on the Pharmacokinetics of Caffeine. Angela E. Joubert, Gary Kamimori, Natalie D. Eddington. Presented at the national meeting of the American Association of Pharmaceutical Scientists 1997

Pharmacokinetic and Pharmacodynamic Effects of Caffeine in Healthy Females during each Phase of the Menstrual Cycle. Donna S. Cox, Tanyifor M. Tohnya, Gary H Kamimori, Ronald Otterstetter, Angela Joubert, Natalie Eddington. Presented at the national meeting of the American Association of Pharmaceutical Scientists 1999

Manuscripts:

The Influence of the Menstrual Cycle on Triazolam and Indocyanine Green Pharmacokinetics. Gary H. Kamimori, Nattee Sirisuth, David J. Greenblatt, Natalie D. Eddington. J Clin Pharmacol (2000) 40: 1-7.

The Effect of the Menstrual Cycle on the Pharmacokinetics of Caffeine in Normal, healthy Eumenorrheic Females. G.H. Kamimori, A. Joubert, R. Otterstetter, M. Santaromana, N.D. Eddington. Eur J Clin Pharmacol (1999) 55: 445-449.

Conclusions

At the present time data collection has been completed and the analyses of all of the biological samples (e.g. drug concentrations, catecholamines, etc.), except those for serum atropine, have been completed. Compilation of the data sets has also been completed. Statistical analysis has been completed on all of the data. Additional manuscripts on the effect of menstrual cycle phase on cognitive performance and mood are in preparation for submission to peer review journals.

FIG. 14

SUBJECTIVE SLEEPINESS SCALE BY PHASE
FOLLOWING 0.25 mg ORAL DOSE OF TRIAZOLAM

FIG. 15

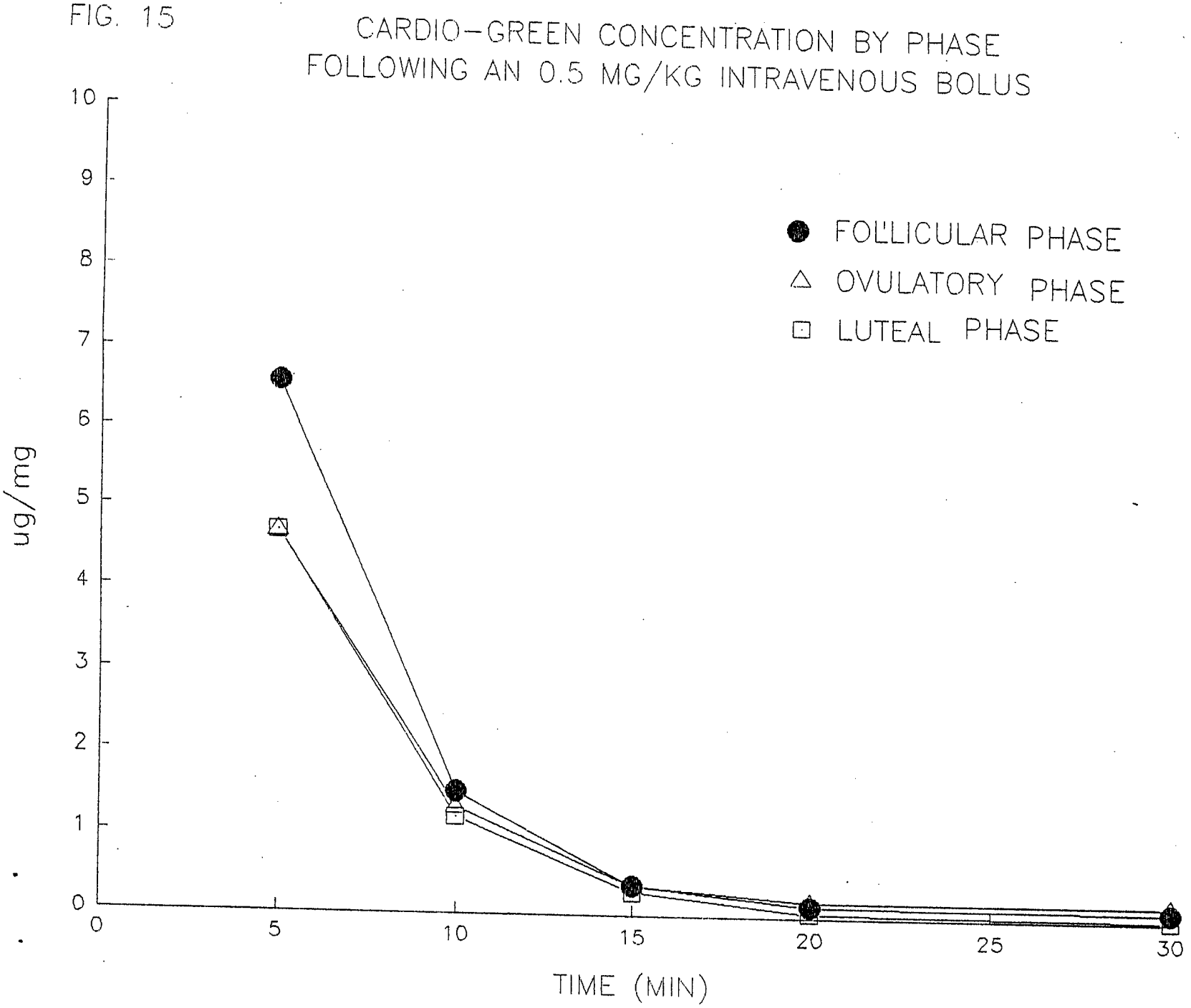

CARDIO-GREEN CONCENTRATION BY PHASE
FOLLOWING AN 0.5 MG/KG INTRAVENOUS BOLUS
FOLLICULAR PHASE
OVULATORY PHASE
LUTEAL PHASE
ug/mg
TIME (MIN)
0
1
2
3
4
5
6
7
8
9
10
0
5
10
15
20
25
30

Table 4: Pharmacokinetic Parameters - ICG

		AUC ($ng/ml*hr^{-1}$)	MRT (hr)	Vd (l)	Cl (L/min)
FOL	X	121.6	3.0	0.84	0.30
	SEM	20.5	0.5	0.13	0.04
OVU	X	78.7	3.2	1.30	0.38
	SEM	3.4	0.1	0.10	0.02
LUT	X	84.5	3.4	1.30	0.36
	SEM	5.0	0.2	0.21	0.02

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APPENDIX A

MAXIMAL EXERCISE STRESS TEST

Appendix A: Maximal Exercise Stress Test

The purpose of a GXT is to determine physiological responses to a controlled exercise stress. For this study, the GXT will serve both a diagnostic and functional objective. The GXT will assess maximal oxygen consumption and check for any cardiovascular problems which may not have been previously identified.

Pretest: Subjects are required to avoid eating food four (4) hours prior to testing. Further, they must abstain from, nicotine products, alcohol, caffeine, both prescription and over-the-counter drugs, and heavy physical exertion for at least twelve (12) hours prior to testing. The subjects should also wear clothing that permits unrestricted movement, are comfortable for exercise, and allow for placement of limb and torso electrodes.

Cycle Adjustments: A electronically braked Bosch 5000 cycle ergometer, with toe straps, will be used for this study. Seat height will be adjusted so that the subject's knee is slightly flexed when the foot is at the bottom of the pedal swing and parallel to the floor.

Metabolic/Respiratory Measurement: An Alpha Technologies Model 4400 metabolic cart will be used to collect expired air. The cart will be calibrated before each test according to the system's operating manual using reference gas of known concentration, volume, and temperature. Heart rate will be recorded using a Sensormedics ECG Monitoring System and 12-lead electrode configuration. Blood pressure will be measured using auscultatory methods with a stethoscope and aneroid sphygmomanometer.

Test Protocol: The cycle ergometer protocol will begin with an unloaded three (3) minute warm-up phase, followed by progressive increases of 25 watts every two (2) minutes. An initial workload of 50-150 watts will be established based on the self-reported fitness level of the subject. Blood pressure will be obtained in the middle of each stage and heart rate will be determined from the ECG tracing taken at the end of each stage.

Test Termination: The test will be terminated when the subject is unable to maintain the required pedal cadence or upon volitional fatigue. The test will be deemed accurate and valid if any combination of the following criteria are met: the patient was unable to continue exercise, a plateau in oxygen consumption occurred concomitant with an increase in workload, a respiratory exchange ratio greater than 1.15, heart rate failed to increase with an increase in workload, and the subject's heart rate was within 10 bpm of their age predicted maximum.

APPENDIX B

COGNITIVE TASKS, MOOD ASSESSMENT, AND SUBJECTIVE MEASURES

Appendix B: Cognitive Tasks, Mood Assessment, and Subjective Measures

The PAB is a subset of the Walter Reed Performance Assessment Battery (Thorne et al, 1985), and various versions are in use currently at numerous Department of Defense research laboratories, hospitals and universities across the country. The PAB is designed as a research tool for following performance over time or treatments. Test items and visual stimuli are presented via microcomputer. Individual tests are automatically generated, administered, recorded, and scored.

Subjective Status will be measured by a standardized test designed to provide self-ratings of mood states and alertness. The Profile of Mood States (POMS) (McNair et al, 1981) is a 65 item adjective checklist that measures current states along 6 subscales: tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment.

Sustained Attention is assessed by the Serial Addition/Subtraction Task adapted from Pauli as used by Wever (Wever, 1979, 1981). This task is a machine-paced mental arithmetic task requiring sustained attention and concentration. Two randomly selected digits and either a plus or minus sign are displayed sequentially in the same center screen location followed by a prompt symbol (?). The subject performs the indicated addition or subtraction and enters the least significant digit of the result. If the result is negative, he/she first adds 10 to it and enters the single positive digit remainder. The digits and signs are each presented for 250 milliseconds, separated by 200 milliseconds with the next trial beginning 500 milliseconds after the response. The task ends after 50 responses and typically takes 3 to 4 minutes.

Logical Reasoning is measured by a task adapted from Baddeley (1968). The letter pair AB or BA is presented along with a statement that correctly or incorrectly describes the order of the letters within the pair (e.g., "B follows A", or "A is not preceded by B"). The subject decides whether the statement is true (same) or false (different) and presses the "S" or "D" key accordingly. The 32 possible permutations are presented once each in random order.

Reaction Time is measured using the 10-Choice Reaction Time task. This test is a visual-motor task requiring subjects to press numerical pad keys that correspond to numbers (choice reaction). The choice reaction time task presents the digits 0 through 9 one at a time in the center of the screen. The stimulus remains until a response is made. The task ends after 50 responses. This task was designed to fulfill the requirements of a standard reaction time task while closely resembling the physical requirements of the Serial Add/Subtract task. The results can therefore be used to correct for certain learning effects in the arithmetic task.

Response interference is measured using the stroop task. This is a test of response competition due to perceptual/linguistic interference. In this task, color (ie green, red, etc.) words or neutral words (i.e. boat, house, etc) appear in the middle of the screen in red, blue, or green letters. The subject has to press a color-coded key (green, red, or blue), which represents the color of the **letters** of the word. The task ends after 50 responses.

Visual spatial rotation was measured using the manikin task. In this task, a man holds in one hand a red square and in the other hand a green circle. Around the outside of the figure is either a green circle or a red square. The subject is to figure out which hand the man is holding the shape that is outlined on the screen and enter the response on two keys pre-assigned as right or left. The man can be face forward, face backwards, right side up, up side down or a combination of these. The task ends after 16 responses.

APPENDIX C

5\15\96

COLLECTION ITINERARY KEY

ATRO	ATROPINE
TRI	TRIAZOLAM
ICG	CARDIO GREEN
CAF	CAFFEINE
CAT	CATECHOLAMINE
HOR	PROGESTERONE AND ESTROGEN
HR/BP	HEART RATE AND BLOOD PRESSURE
MIT	CORTISOL, ALDOSTERONE, OSMOLALITY, Na K
C	CORTISOL
FFA	FREE FATTY ACIDS, GLUCOSE, HEMATOCRIT, HEMOGLOBIN
PC	ACETYLCHOLINESTERASE AND BUTYLCHOLINESTERASE

ATROPINE COLLECTION ITINERARY

Name:_____ ID: _____ Date: _____

Phase: _____ Trial: (1) (2) (3) **Serum Test

Pre-Administration

Actual	Planned	
_____	-00:30	SUBJECT PREP. PAB (11), PAB (12)
_____	-00:05	ATRO (1), CAT (1), HOR (1), MIT (1), FFA (1), PC (1), HR\BP (1), PAB (13)

Administration

_____	00:00	DRUG ADMINISTRATION
_____	00:15	ATRO (2)
_____	00:30	ATRO (3), CAT (2), MIT (2), FFA (2), HR\BP (2)
_____	00:45	ATRO (4)
_____	01:00	ATRO (5), CAT (3), MIT (3), FFA (3), PC (2),HR\BP (3), PAB (14)
_____	01:30	ATRO (6), CAT (4), HR\BP (4)
_____	02:00	ATRO (7), CAT (5), MIT (4), FFA (4), PC (3), HR\BP (5), PAB (15)
_____	03:00	HR\BP (6)
_____	04:00	ATRO (8), CAT (6), MIT (5), FFA (5), HR\BP (7), PAB (16)
_____	04:05	LUNCH
_____	06:00	ATRO (9), CAT (7), PC (4), HR\BP (8), PAB (17)
_____	08:00	ATRO (10), CAT (8), MIT (6), FFA (6), HR\BP (9), PAB (18)
_____	09:00	DINNER
_____	10:00	ATRO (11), CAT (9), PC (5), HR\BP (10), PAB (19)
_____	12:00	ATRO (12), CAT (10), PAB (20), HR\BP (11)

CAFFEINE COLLECTION ITINERARY

Name:_____ ID: _____ Date: _____

Phase: _____ Trial: (1) (2) (3) **Serum Test

Pre-Administration

Actual	Planned	
_____	-00:30	SUBJECT PREP, PAB (11) PAB (12)
_____	-00:10	CAF (1), CAT (1), HOR (1), MIT (1), FFA(1), PAB (13), HR\BP (1)

Administration

_____	00:00	Drug Administration
_____	00:15	CAFF (2)
_____	00:30	CAFF (3), CAT (2), MIT (2), FFA (2), HR\BP (2)
_____	00:45	CAFF (4)
_____	01:00	CAFF (5), CAT (3), MIT (3), FFA (3), HR\BP (3), PAB (14)
_____	01:30	CAFF (6), CAT (4), HR\BP (4)
_____	02:00	CAFF(7), CAT (5), MIT (4), FFA (4), HR\BP (5), PAB (15)
_____	03:00	HR\BP (6)
_____	04:00	CAFF (8), CAT (6), MIT (5), FFA(5), HR\BP (7), PAB (16),
_____	04:05	LUNCH
_____	06:00	CAFF (9), HR\BP (8), PAB (17)
_____	08:00	CAFF (10), CAT (7), MIT (6), FFA (6), HR\BP (9), PAB (18),
_____	09:00	DINNER
_____	10:00	CAFF (11), HR\BP (10), PAB (19)
_____	12:00	CAFF (12), CAT (8), HR\BP (11), PAB (20)

REV 06/11/96

TRIAZOLAM \ ICG COLLECTION ITINERARY

Name:_____ ID: _____ Date: _____

Phase: _____ Trial: (1) (2) (3) **Serum Test

Pre-Administration

Actual	Planned	
_____	-00:60	SUBJ PREP, PAB (11), PAB (12), RRT PRACTICE (FIRST TRIAL ONLY)
_____	-00:30	ICG (1), TRI (1), CAT (1), HOR (1), HR\BP (1), C(1), PC (1) PAB(13), ESTT(1)

Administration

_____	00:00	DRUG ADMINISTRATION
_____	00:05	ICG (2)
_____	00:10	ICG (3)
_____	00:15	ICG (4)
_____	00:20	ICG (5),ESTT(2)
_____	00:30	ICG (6),RRT(1)

Administration

_____	00:00	DRUG ADMINISTRATION
_____	00:15	TRI (2)
_____	00:30	TRI (3), CAT(2), HR\BP (2), C (2)
_____	00:45	TRI (4)
_____	01:00	TRI (5), CAT (3), HR\BP (3), C (3), PC (2)
_____	01:20	WAKE UP SUBJECT
_____	01:30	TRI (6), CAT (4), HR\BP (4), RESTRICTED RECALL, PAB (14)
_____	02:00	TRI (7), CAT (5), HR\BP (5), C (4), PC (3), ESTT(3)
_____	02:30	ESTT(4)
_____	03:00	PAB (15), ESTT (5)
_____	03:30	ESTT(6) LUNCH
_____	04:00	TRI (8), CAT (6), HR\BP (6), C(5), ESTT(7)
_____	05:00	ESTT(8)

_____	06:00	TRI (9), CAT (7), HR\BP (7). PC (4). PAB (16). ESTT(9)
_____	08:00	TRI (10), CAT (8), HR\BP (8). C(6). ESTT(10)
_____	08:30	DINNER
_____	09:00	PAB (17)
_____	10:00	TRI (11). CAT (9). HR\BP (9). PC (5). ESTT(11)

APPENDIX D

Table 5: Caffeine Concentration - Caffeine (µg/ml)

	Time	PRE	15 min	30 min	45 min	1 HR	1.5 HR	2HR	4 HR	6 HR	8 HR	10 HR	12 HR
FOL	X	0.0	2.6	4.8	6.1	6.5	6.8	6.6	5.6	4.9	4.0	2.8	2.2
	SEM	0.0	0.3	0.4	0.6	0.4	0.5	0.5	0.4	0.6	0.5	0.5	0.2
OVU	X	0.0	3.6	6.8	7.3	7.1	7.4	7.1	6.1	5.5	4.3	3.3	3.1
	SEM	0.0	0.5	1.3	0.7	0.6	0.6	0.6	0.6	0.4	0.5	0.4	0.3
LUT	X	0.0	3.5	4.7	5.8	6.0	6.7	6.1	5.1	4.5	3.8	3.1	2.8
	SEM	0.0	0.5	0.6	0.7	0.6	0.7	0.7	0.5	0.6	0.4	0.3	0.4

Table 6: Aldosterone - Caffeine - (pmol/L)

	Time	PRE	30 HR	1 HR	2 HR	4 HR	8 HR
FOL	X	300.8	269.6	185.0	124.5	121.5	114.5
	SEM	49.0	69.0	50.4	28.4	15.5	14.9
OVU	X	297.7	256.0	216.3	168.6	124.7	116.9
	SEM	59.6	56.2	31.6	18.8	13.1	12.5
LUT	X	356.7	281.3	222.6	220.3	207.1	161.5
	SEM	38.8	35.4	20.8	34.4	26.2	24.1

Table 7: Epinephrine Concentration - Caffeine - (ug/mL)

	Time	PRE	30 MIN	1 HR	1:30 HR	2 HR	4 HR	8 HR	12 HR
FOL	X	181.3	178.8	136.8	94.4	127.6	141.7	110.1	81.1
	SEM	98.3	102.2	64.7	22.4	45.9	85.5	41.2	17.0
OVU	X	59.9	45.7	55.0	67.2	54.8	54.9	58.8	45.3
	SEM	15.9	7.8	8.1	8.6	13.8	10.0	8.5	7.0
LUT	X	84.3	42.3	44.3	45.4	45.8	88.0	80.5	76.9
	SEM	38.7	12.7	22.5	14.4	13.3	33.8	46.9	40.0

Norepinephrine Concentration - Caffeine - (ug/mL)

	Time	PRE	30 MIN	1 HR	1:30 HR	2 HR	4 HR	8 HR	12 HR
FOL	X	350.7	299.4	285.4	293.8	350.8	278.4	296.7	321.8
	SEM	54.7	26.6	17.9	52.2	63.8	34.9	50.5	34.5
OVU	X	251.4	249.2	258.8	257.5	255.5	222.3	194.8	191.2
	SEM	22.0	19.7	24.0	25.6	20.6	23.1	14.3	14.4
LUT	X	341.3	354.4	338.0	314.0	263.7	297.9	274.5	172.8
	SEM	37.6	47.4	32.3	31.3	51.1	34.5	42.2	25.2

Table 8: Heart Rate - Caffeine (BPM)

	Time	PRE	30 MIN	1 HR	1:30 HR	2 HR	3 HR	4 HR	6 HR	8 HR	10 HR	12 HR
FOL	X	68.8	68.5	67.0	68.6	70.1	65.7	66.2	71.8	67.2	69.6	70.3
	SEM	2.4	3.0	3.6	3.5	3.9	2.6	3.4	2.2	3.0	3.0	2.6
OVU	X	69.6	65.8	64.5	66.3	65.7	63.9	64.9	70.1	67.4	71.6	69.0
	SEM	2.7	3.8	2.9	2.5	2.2	2.6	2.4	2.1	2.2	2.6	1.9
LUT	X	65.0	63.1	64.4	63.7	65.0	64.5	64.7	70.1	70.3	70.8	69.8
	SEM	2.5	2.3	2.5	2.3	2.5	3.0	3.6	2.3	2.2	2.6	2.6

Rate Pressure Product - Caffeine ((SBP*BPM)/100)

	Time	PRE	30 MIN	1 HR	1:30 HR	2 HR	3 HR	4 HR	6 HR	8 HR	10 HR	12 HR
FOL	X	75.6	73.9	71.9	74.4	74.4	71.1	66.9	72.4	66.4	70.6	71.3
	SEM	3.7	4.5	4.5	4.8	5.3	2.8	4.6	2.8	3.6	3.3	3.3
OVU	X	72.1	69.1	69.0	67.7	67.0	64.8	66.6	72.4	71.1	74.7	71.6
	SEM	4.6	5.1	3.5	3.5	3.3	3.0	3.3	3.6	3.3	3.9	3.3
LUT	X	69.6	66.5	70.1	71.4	68.4	66.1	67.0	73.4	73.6	68.6	70.1
	SEM	4.5	4.2	4.3	4.3	4.0	4.7	6.1	2.9	3.7	2.3	2.6

Table 9: Systolic Blood Pressure - Caffeine (mm Hg)

	Time	PRE	30 MIN	1 HR	1:30 HR	2 HR	3 HR	4 HR	6 HR	8 HR	10 HR	12 HR
FOL	X	112.6	111.5	111.2	111.4	110.4	109.0	104.3	104.0	101.0	103.6	103.8
	SEM	3.1	4.4	3.8	3.8	2.2	2.3	1.9	3.1	1.7	2.8	2.7
OVU	X	104.4	104.4	106.9	102.0	101.5	101.5	102.3	102.9	105.8	103.9	103.5
	SEM	3.2	3.1	2.7	3.0	2.8	2.6	2.4	3.3	3.9	2.6	2.6
LUT	X	107.3	106.9	108.7	111.3	106.9	102.6	105.5	105.6	103.7	101.3	103.6
	SEM	3.5	3.5	3.9	3.5	2.7	2.9	3.3	2.3	2.5	2.6	2.5

Diastolic Blood Pressure - Caffeine (mm Hg)

	Time	PRE	30 MIN	1 HR	1:30 HR	2 HR	3 HR	4 HR	6 HR	8 HR	10 HR	12 HR
FOL	X	68.2	68.2	67.6	70.4	65.6	69.8	63.2	59.8	65.4	61.8	59.6
	SEM	2.6	1.9	2.0	2.9	2.1	3.2	2.3	1.3	1.6	3.0	1.8
OVU	X	65.3	65.6	69.3	67.3	63.3	60.2	62.1	61.2	60.3	61.6	60.9
	SEM	2.3	2.1	2.3	3.2	2.2	2.5	1.6	1.2	2.1	1.2	1.0
LUT	X	66.4	69.1	67.1	65.5	64.0	64.0	63.2	60.2	62.2	61.5	61.7
	SEM	2.9	2.5	3.0	1.9	2.0	2.5	1.4	1.3	1.3	1.8	1.8

Table 10: Glucose Concentration - Caffeine (µg/ml)

	Time	PRE	30 MIN	1 HR	2 HR	4 HR	8 HR
FOL	X	4.7	4.4	4.5	4.4	4.6	5.2
	SEM	0.2	0.2	0.2	0.1	0.1	0.1
OVU	X	4.7	4.6	4.6	4.5	4.6	5.2
	SEM	0.3	0.2	0.1	0.1	0.1	0.2
LUT	X	4.3	4.0	4.2	4.3	4.3	4.8
	SEM	0.2	0.1	0.1	0.1	0.1	0.2

Free Fatty Acid - Caffeine (mmol)

	Time	PRE	30 HR	1 HR	2 HR	4 HR	8 HR
FOL	X	0.3	0.3	0.4	0.4	0.5	0.3
	SEM	0.0	0.0	0.1	0.1	0.0	0.0
OVU	X	0.4	0.4	0.4	0.5	0.6	0.3
	SEM	0.0	0.1	0.1	0.1	0.1	0.0
LUT	X	0.4	0.5	0.6	0.7	0.8	0.3
	SEM	0.0	0.1	0.1	0.1	0.1	0.0

Table 11: Hematocrit - Caffeine (%)

	Time	PRE	30 HR	1 HR	2 HR	4 HR	8 HR
FOL	X	33.7	34.7	34.9	34.3	34.7	33.7
	SEM	1.1	0.6	0.6	0.8	0.7	0.6
OVU	X	35.3	35.3	35.9	35.0	35.6	34.8
	SEM	0.9	0.9	1.0	0.9	0.9	0.7
LUT	X	35.9	35.3	35.1	35.3	35.1	34.8
	SEM	0.9	1.1	0.9	0.9	1.0	0.8

Hemoglobin - Caffeine (g/dL)

	Time	PRE	30 HR	1 HR	2 HR	4 HR	8 HR
FOL	X	11.8	11.6	11.6	11.4	12.3	12.3
	SEM	0.4	0.4	0.4	0.3	0.3	0.4
OVU	X	11.9	11.8	11.8	11.9	11.9	12.2
	SEM	0.3	0.4	0.4	0.4	0.4	0.6
LUT	X	12.3	12.3	12.3	12.3	12.4	12.8
	SEM	0.5	0.5	0.5	0.5	0.6	0.6

Table 12: Plasma Protein - Caffeine (mg %)

	Time	PRE	30 HR	1 HR	2 HR	4 HR	8 HR
FOL	X	38.1	37.8	38.1	38.0	38.3	37.4
	SEM	0.7	0.3	0.5	0.5	0.4	0.5
OVU	X	39.0	38.7	39.0	38.8	39.4	38.2
	SEM	0.6	0.5	0.5	0.6	0.7	0.7
LUT	X	39.3	38.6	38.8	39.6	39.0	38.3
	SEM	0.6	0.5	0.5	0.7	0.7	0.5

Plasma Volume Change - Caffeine - % Change

	Time	30 MIN	1 HR	2 HR	4 HR	8 HR
FOL	X	-0.2	-0.7	2.1	-5.4	-2.6
	SEM	-2.8	-1.9	1.9	-3.2	-3.8
OVU	X	1.4	0.2	1.1	0.4	0.5
	SEM	1.4	1.7	1.6	2.1	4.0
LUT	X	1.4	1.1	1.4	0.9	-1.4
	SEM	2.2	1.6	2.6	2.9	-2.7

Table 13: Sodium - Caffeine (mEq/L)

	Time	PRE	30 HR	1 HR	2 HR	4 HR	8 HR
FOL	X	134.5	135.6	135.0	136.3	136.0	137.0
	SEM	1.5	1.4	1.3	1.0	1.3	1.5
OVU	X	136.8	137.4	137.3	138.1	136.9	137.1
	SEM	1.1	1.5	1.3	1.9	1.6	1.7
LUT	X	135.1	135.5	134.2	134.6	133.8	134.8
	SEM	0.6	1.3	1.3	0.6	1.0	1.4

Potassium - Caffeine (mEq/L)

	Time	PRE	30 HR	1 HR	2 HR	4 HR	8 HR
FOL	X	3.4	3.6	3.5	3.5	3.6	3.6
	SEM	0.1	0.1	0.0	0.0	0.1	0.1
OVU	X	3.6	3.7	3.7	3.8	3.8	3.7
	SEM	0.1	0.1	0.1	0.1	0.1	0.1
LUT	X	3.7	3.7	3.6	3.6	3.5	3.5
	SEM	0.1	0.1	0.1	0.1	0.1	0.1

Osmolality - Caffeine (mOsm/Kg)

	Time	PRE	30 HR	1 HR	2 HR	4 HR	8 HR
FOL	X	278.1	279.5	277.3	279.1	278.1	278.8
	SEM	2.2	1.8	2.1	1.3	1.6	2.8
OVU	X	278.9	279.9	280.9	280.6	279.4	283.1
	SEM	1.7	1.9	1.5	1.3	1.7	1.6
LUT	X	277.3	278.8	277.5	277.8	275.5	278.2
	SEM	1.2	2.2	1.3	1.9	1.4	1.2

Table 14: Serial +/- Accuracy -Caffeine (%)

	Time	PRE	1 HR	2 HR	4HR	6 HR	8 HR	10 HR	12 HR
FOL	X	97.0	97.0	97.4	98.6	97.4	98.0	97.4	96.8
	SEM	1.1	1.0	0.7	0.3	0.9	0.9	0.9	0.9
OVU	X	97.8	96.0	97.5	97.8	98.2	98.2	97.8	97.6
	SEM	0.6	1.1	0.9	0.8	0.8	0.6	0.8	0.9
LUT	X	95.5	97.5	97.5	97.3	96.7	98.0	96.7	97.5
	SEM	1.9	1.2	0.6	0.7	1.1	0.6	1.0	0.8

Serial +/- Speed-Caffeine (resp/min)

	Time	PRE	1 HR	2 HR	4HR	6 HR	8 HR	10 HR	12 HR
FOL	X	93.1	109.7	112.8	117.0	114.5	112.7	114.7	111.0
	SEM	20.0	23.7	18.5	27.1	23.5	22.5	26.3	21.2
OVU	X	97.6	107.1	122.5	115.5	123.0	104.8	101.1	121.4
	SEM	17.7	12.7	17.4	17.5	16.9	13.2	18.4	13.5
LUT	X	107.1	109.0	115.9	115.8	120.3	114.2	113.5	114.3
	SEM	19.3	16.5	11.8	16.7	16.2	13.9	16.8	15.7

Serial +/- Throughput- Caffeine (speed*accuracy)

	Time	PRE	1 HR	2 HR	4HR	6 HR	8 HR	10 HR	12 HR
FOL	X	91.3	107.2	110.3	115.8	112.3	110.1	112.0	108.1
	SEM	20.3	24.0	18.8	27.2	23.7	22.0	25.9	21.4
OVU	X	97.4	104.3	117.5	113.8	122.2	102.3	106.2	118.7
	SEM	17.7	12.9	18.0	17.8	17.0	12.8	16.7	13.4
LUT	X	103.6	107.4	113.4	112.5	117.3	112.4	110.6	111.8
	SEM	19.4	16.9	11.9	16.2	16.6	14.2	17.1	15.8

Table 15: Choice Reaction Accuracy - Caffeine (%)

	Time	PRE	1 HR	2 HR	4HR	6 HR	8 HR	10 HR	12 HR
FOL	X	98.8	99.0	98.8	98.8	98.8	99.2	98.0	99.2
	SEM	0.7	0.3	0.5	0.6	0.4	0.4	0.6	0.4
OVU	X	97.2	98.2	98.4	99.6	99.3	99.1	98.7	98.9
	SEM	1.1	0.7	0.5	0.2	0.4	0.4	0.6	0.3
LUT	X	97.6	98.2	97.8	99.3	98.0	98.2	99.3	98.6
	SEM	0.9	0.5	0.7	0.3	0.7	0.6	0.4	0.6

Choice Reaction Speed - Caffeine (resp/min)

	Time	PRE	1 HR	2 HR	4HR	6 HR	8 HR	10 HR	12 HR
FOL	X	105.9	108.8	110.8	107.2	108.2	110.5	106.6	112.8
	SEM	4.7	4.5	3.9	4.6	5.4	5.3	4.9	4.6
OVU	X	107.7	106.1	107.8	109.1	107.7	110.5	109.8	112.8
	SEM	4.4	4.2	4.2	4.2	4.6	4.3	4.6	4.0
LUT	X	106.0	109.1	107.6	106.2	110.4	108.5	107.8	110.9
	SEM	3.8	4.4	3.5	4.3	4.5	3.7	4.4	3.6

Choice Reaction Throughput- Caffeine (speed*accuracy)

	Time	PRE	1 HR	2 HR	4HR	6 HR	8 HR	10 HR	12 HR
FOL	X	104.6	108.8	109.5	106.0	106.9	109.7	104.6	111.9
	SEM	4.7	4.1	4.0	4.7	5.4	5.4	5.1	4.7
OVU	X	105.6	104.1	106.0	108.8	106.8	109.4	108.5	111.6
	SEM	4.0	4.2	4.2	4.3	4.3	4.2	4.7	4.0
LUT	X	103.5	107.1	105.2	105.5	108.2	106.6	107.0	109.2
	SEM	3.7	4.2	3.5	4.3	4.7	3.7	4.3	3.2

Table 16: Logical Reasoning - Accuracy - Caffeine (%)

	Time	PRE	1 HR	2 HR	4HR	6 HR	8 HR	10 HR	12 HR
FOL	X	94.3	94.7	96.9	94.4	93.4	95.0	95.9	94.6
	SEM	2.1	2.2	1.3	2.7	2.2	1.6	1.7	1.8
OVU	X	96.3	94.6	94.3	94.9	95.7	95.7	95.2	92.3
	SEM	2.2	2.4	2.8	2.7	2.8	2.0	2.9	4.4
LUT	X	94.3	95.5	96.3	95.2	94.0	94.9	94.0	94.9
	SEM	3.4	2.2	2.5	1.9	1.8	2.3	3.7	2.5

Logical Reasoning - Speed - Caffeine (resp/min)

	Time	PRE	1 HR	2 HR	4HR	6 HR	8 HR	10 HR	12 HR
FOL	X	25.9	28.8	29.6	29.2	28.6	28.1	28.8	29.9
	SEM	4.9	4.9	4.9	4.3	4.8	4.2	4.0	4.9
OVU	X	27.6	28.5	35.6	30.3	30.8	31.3	30.4	31.9
	SEM	4.0	4.0	6.9	3.7	3.8	4.1	4.3	4.4
LUT	X	25.1	28.3	28.6	30.5	28.7	30.2	30.2	30.5
	SEM	3.7	3.7	3.7	4.0	3.6	3.5	3.9	4.2

Logical Reasoning - Throughput - Caffeine (speed*accuracy)

	Time	PRE	1 HR	2 HR	4HR	6 HR	8 HR	10 HR	12 HR
FOL	X	25.0	27.7	28.9	28.0	27.2	26.9	27.6	28.7
	SEM	5.0	4.9	4.9	4.2	4.9	4.1	4.1	5.0
OVU	X	26.8	27.5	27.9	29.4	30.1	30.5	29.5	30.5
	SEM	4.1	4.0	3.9	3.9	4.0	4.2	4.6	4.6
LUT	X	24.3	27.3	28.0	29.4	27.4	29.1	29.1	29.4
	SEM	3.8	3.8	3.8	4.0	3.8	3.6	4.1	4.3

Table 17: Stroop Accuracy- Caffeine (%)

	Time	PRE	1 HR	2 HR	4HR	6 HR	8 HR	10 HR	12 HR
FOL	X	99.0	98.3	98.5	97.9	97.7	98.5	98.8	98.5
	SEM	0.4	0.5	0.4	0.6	0.7	0.8	0.5	0.4
OVU	X	98.1	98.9	97.7	97.9	98.5	98.7	99.1	98.5
	SEM	0.8	0.5	0.6	0.7	0.7	0.4	0.3	0.5
LUT	X	98.7	97.5	98.7	98.3	97.0	98.1	98.1	98.5
	SEM	0.6	0.8	0.4	0.6	0.7	0.6	0.7	0.5

Stroop Speed - Caffeine (resp/min)

	Time	PRE	1 HR	2 HR	4HR	6 HR	8 HR	10 HR	12 HR
FOL	X	136.1	138.1	134.3	137.9	142.5	139.0	144.5	152.0
	SEM	11.5	7.8	7.5	6.8	6.5	6.9	7.1	11.0
OVU	X	141.7	146.2	140.0	139.1	147.6	151.6	155.1	156.1
	SEM	8.6	10.0	8.1	9.5	8.5	8.6	10.4	11.3
LUT	X	147.3	146.1	148.3	140.4	147.4	154.2	153.9	156.4
	SEM	14.1	8.9	12.9	8.5	10.3	13.1	10.1	11.5

Stroop Throughput - Caffeine (speed*accuracy)

	Time	PRE	1 HR	2 HR	4HR	6 HR	8 HR	10 HR	12 HR
FOL	X	135.1	135.7	132.3	134.9	139.3	137.1	142.7	145.6
	SEM	11.6	7.6	7.3	6.5	6.6	7.2	7.0	12.0
OVU	X	139.1	144.3	136.5	136.0	145.3	149.3	153.7	153.7
	SEM	8.6	9.5	7.4	8.8	8.1	8.1	10.4	11.1
LUT	X	145.3	142.9	146.3	137.9	143.0	151.5	150.8	154.0
	SEM	14.1	9.5	12.6	8.4	10.2	13.3	9.8	11.3

Table 18: Manikin Accuracy - Caffeine (%)

	Time	PRE	1 HR	2 HR	4HR	6 HR	8 HR	10 HR	12 HR
FOL	X	97.5	97.5	96.3	96.9	98.1	100.0	97.5	99.4
	SEM	1.4	1.9	1.9	1.9	1.0	0.0	1.4	0.6
OVU	X	97.2	99.4	98.9	98.9	97.7	98.9	99.4	97.7
	SEM	1.3	0.6	0.8	0.8	1.0	1.1	0.6	1.0
LUT	X	96.6	97.7	98.9	98.9	97.2	97.7	99.4	97.7
	SEM	1.8	1.3	0.8	0.8	1.0	1.0	0.6	1.0

Manikin Speed - Caffeine (resp/min)

	Time	PRE	1 HR	2 HR	4HR	6 HR	8 HR	10 HR	12 HR
FOL	X	56.8	61.0	60.2	59.7	63.3	63.8	62.1	63.5
	SEM	7.5	7.9	6.7	7.6	7.3	6.9	6.9	6.9
OVU	X	60.3	63.1	64.8	64.5	64.3	65.6	62.8	65.2
	SEM	4.3	5.8	4.5	5.4	5.1	5.7	4.9	4.7
LUT	X	60.8	58.6	59.9	59.4	62.7	60.4	62.7	60.3
	SEM	5.0	4.2	4.5	5.0	5.3	5.1	5.5	5.2

Manikin Throughput - Caffeine (speed*accuracy)

	Time	PRE	1 HR	2 HR	4HR	6 HR	8 HR	10 HR	12 HR
FOL	X	55.6	60.5	59.0	57.5	62.4	63.0	60.6	63.3
	SEM	7.6	8.2	6.7	7.8	7.3	6.9	6.9	7.0
OVU	X	59.2	62.7	36.9	63.9	63.0	64.8	62.5	63.7
	SEM	4.2	5.8	4.3	5.5	4.8	5.6	4.9	4.7
LUT	X	58.8	57.3	59.4	58.7	61.1	59.2	62.3	58.9
	SEM	5.1	4.2	4.7	4.9	5.3	5.3	5.5	4.9

Table 19: Sleep Scale - Caffeine

	Time	PRE	1 HR	2 HR	4HR	6 HR	8 HR	10 HR	12 HR
FOL	X	2.6	2.1	1.9	2.0	2.2	2.1	2.0	2.0
	SEM	0.3	0.4	0.3	0.3	0.3	0.2	0.2	0.2
OVU	X	2.3	1.8	2.2	2.0	2.4	2.3	2.3	2.0
	SEM	0.4	0.3	0.2	0.2	0.3	0.3	0.4	0.3
LUT	X	2.1	2.1	1.9	2.3	2.2	2.2	2.1	2.0
	SEM	0.3	0.2	0.3	0.3	0.3	0.3	0.3	0.2

Table 20: POMS - Tension - Caffeine

	Time	PRE	1 HR	2 HR	4HR	6 HR	8 HR	10 HR	12 HR
FOL	X	11.4	13.6	18.6	14.5	12.5	14.7	13.1	13.6
	SEM	3.9	5.4	6.1	4.7	4.1	4.7	4.1	4.5
OVU	X	9.3	11.4	9.3	7.8	8.8	9.3	8.8	11.4
	SEM	3.0	3.9	3.4	3.1	3.8	3.0	2.8	3.3
LUT	X	9.9	12.1	13.6	11.4	10.6	9.6	9.3	11.1
	SEM	3.7	3.5	4.1	4.5	4.8	3.0	3.5	4.0

POMS - Depression - Caffeine

	Time	PRE	1 HR	2 HR	4HR	6 HR	8 HR	10 HR	12 HR
FOL	X	2.2	1.0	0.8	1.5	1.2	2.5	1.5	1.2
	SEM	1.1	0.5	0.5	1.0	0.6	1.3	0.8	0.7
OVU	X	2.3	1.5	3.3	2.1	1.7	1.5	0.8	1.5
	SEM	1.0	0.6	1.8	1.0	0.7	0.7	0.4	0.6
LUT	X	1.1	0.9	0.6	1.8	0.8	0.6	0.8	0.8
	SEM	0.5	0.4	0.3	1.1	0.4	0.3	0.6	0.6

POMS - Anger - Caffeine

	Time	PRE	1 HR	2 HR	4HR	6 HR	8 HR	10 HR	12 HR
FOL	X	2.1	1.8	2.2	3.1	2.2	1.9	1.6	2.3
	SEM	1.7	1.3	1.3	1.5	1.7	1.3	1.3	1.6
OVU	X	2.1	1.9	2.5	2.1	1.3	0.8	2.5	1.9
	SEM	1.1	1.2	1.8	1.2	0.8	0.6	1.3	1.5
LUT	X	1.5	1.1	0.4	2.3	1.7	2.3	0.8	1.3
	SEM	0.7	0.7	0.3	1.9	1.3	1.6	0.4	1.0

Table 21: POMS - Vigor- Caffeine

	Time	PRE	1 HR	2 HR	4HR	6 HR	8 HR	10 HR	12
FOL	X	45.9	50.3	49.7	45.9	43.8	46.6	44.7	46
	SEM	8.1	6.9	7.1	6.5	7.8	7.1	6.4	6.
OVU	X	44.3	41.5	43.2	46.3	44.9	42.9	40.3	44
	SEM	7.0	5.5	5.7	6.4	7.4	6.7	7.3	7.
LUT	X	51.4	49.4	52.8	48.0	46.9	44.6	45.7	47.
	SEM	6.9	6.1	7.4	8.3	5.9	7.4	7.8	6.

POMS - Fatigue - Caffeine

	Time	PRE	1 HR	2 HR	4HR	6 HR	8 HR	10 HR	12 H
FOL	X	18.6	12.9	12.5	13.9	11.8	15.0	15.4	21.
	SEM	7.2	5.5	6.7	6.3	5.7	5.7	5.3	7.
OVU	X	12.3	12.3	12.0	11.7	12.7	13.6	16.6	13.
	SEM	5.9	6.0	5.9	5.9	5.3	5.0	5.6	5.
LUT	X	12.9	14.3	14.6	14.4	16.2	13.9	19.5	19.
	SEM	5.6	5.3	5.4	5.6	6.0	5.2	6.9	6.4

POMS - Confusion - Caffeine

	Time	PRE	1 HR	2 HR	4HR	6 HR	8 HR	10 HR	12 H
FOL	X	13.2	10.7	13.2	15.0	12.9	15.4	15.4	15.
	SEM	4.9	4.5	4.3	5.3	4.1	4.7	4.3	4.1
OVU	X	12.3	14.6	13.6	13.9	14.3	15.3	13.3	14.
	SEM	3.6	4.2	3.7	3.7	4.1	4.1	3.6	4.3
LUT	X	13.3	12.9	12.3	13.3	13.9	12.9	14.9	12.
	SEM	3.5	3.4	4.5	4.4	3.6	3.7	3.7	3.6

Table 22: Aldosterone - Atropine - (pmol/L)

	Time	PRE	30 HR	1 HR	2 HR	4 HR	8 HR
FOL	X	230.3	200.5	219.3	142.5	142.8	139.2
	SEM	71.4	69.5	76.8	52.7	26.2	37.5
OVU	X	263.5	159.2	121.7	96.9	125.7	141.6
	SEM	46.9	38.3	31.2	16.7	23.3	25.6
LUT	X	526.5	297.5	237.7	174.1	264.1	367.0
	SEM	59.5	36.8	39.0	39.9	94.2	112.5

Table 23: Epinephrine Concentration - Atropine - (ug/mL)

	Time	PRE	30 MIN	1 HR	1:30 HR	2 HR	4 HR	6 HR	8 HR	10 HR	12 HR
FOL	X	56.8	54. 2	49.4	56.6	55.2	34.8	51.7	39.4	43.4	59.5
	SEM	17.7	23.3	21.9	19.3	12.1	12.1	10.3	10.0	9.3	10.6
OVU	X	46.0	134.6	70.3	65.3	24.9	34.4	20.5	39.0	43.7	43.2
	SEM	10.8	100.7	48.8	42.2	9.2	10.5	7.9	9.7	10.7	9.2
LUT	X	59.3	80.1	50.9	72.6	78.2	47.4	45.2	43.9	54.2	80.1
	SEM	26.7	27.4	9.9	3.1	9.6	6.5	11.9	5.5	4.6	21.8

Norepinephrine Concentration - Atropine - (ug/mL)

	Time	PRE	30 MIN	1 HR	1:30 HR	2 HR	4 HR	6 HR	8 HR	10 HR	12 HR
FOL	X	306.8	198.8	177.9	205.0	203.1	171.7	190.2	218.3	152.0	157.7
	SEM	57.7	24.6	19.8	21.0	25.4	20.8	25.8	49.0	21.1	21.9
OVU	X	272.2	164.3	153.5	66.4	146.1	172.7	202.5	173.0	186.9	137.6
	SEM	45.1	39.5	16.0	26.1	12.1	20.2	13.6	28.8	21.6	25.6
LUT	X	319.5	329.0	239.8	238.3	223.6	229.5	224.9	232.9	252.1	210.3
	SEM	42.3	88.7	37.0	44.4	24.2	14.7	14.9	22.1	43.3	13.3

Table 24: Heart Rate - Atropine (bpm)

	Time	PRE	30 MIN	1 HR	1:30 HR	2 HR	3 HR	4 HR	6 HR	8 HR	10 HR	12 HR
FOL	X	67.0	101.2	100.9	94.6	89.3	78.0	73.2	72.2	65.8	64.4	65.7
	SEM	2.4	4.1	3.3	2.9	2.9	3.0	3.5	3.0	3.1	2.0	2.4
OVU	X	64.7	94.3	94.8	92.8	88.3	79.7	71.4	70.9	65.3	67.5	66.0
	SEM	0.9	3.1	2.6	2.8	2.2	3.1	2.2	1.3	2.0	2.2	2.3
LUT	X	69.6	102.5	101.5	92.3	89.5	80.3	75.2	72.7	68.8	66.8	68.4
	SEM	2.0	3.5	3.6	2.9	2.8	2.9	3.0	1.7	2.3	3.1	3.2

Rate Pressure Product - Atropine ((SBP*HR)/100)

	Time	PRE	30 MIN	1 HR	1:30 HR	2 HR	3 HR	4 HR	6 HR	8 HR	10 HR	12 HR
FOL	X	72.7	105.2	115.9	96.7	98.5	81.1	75.3	71.8	63.3	64.8	57.7
	SEM	3.4	9.9	5.7	9.3	2.6	3.8	3.9	4.0	3.5	3.0	6.0
OVU	X	71.0	108.7	110.8	105.9	98.4	88.3	75.1	70.8	62.6	65.8	65.6
	SEM	2.6	5.8	5.2	4.9	4.6	5.7	3.8	3.0	3.6	2.9	3.1
LUT	X	76.2	113.5	108.3	94.5	94.3	81.3	72.1	71.1	68.0	66.6	68.3
	SEM	3.1	6.2	5.8	5.0	4.6	4.0	3.7	2.2	3.2	4.2	4.7

Table 25: Systolic Blood Pressure - Atropine (mm Hg)

	Time	PRE	30 MIN	1 HR	1:30 HR	2 HR	3 HR	4 HR	6 HR	8 HR	10 HR	12 HR
FOL	X	108.2	115.5	114.5	111.8	110.8	103.8	102.9	98.9	96.0	100.4	96.9
	SEM	2.6	3.6	3.4	2.4	2.8	2.3	2.3	2.2	1.4	2.6	1.7
OVU	X	109.7	113.7	114.5	113.2	110.2	108.8	104.8	99.3	96.4	96.2	99.0
	SEM	2.8	3.0	3.3	3.0	3.1	3.6	3.5	3.0	3.1	2.5	2.6
LUT	X	109.3	110.2	106.2	101.8	105.0	101.0	95.7	98.0	98.7	99.3	99.0
	SEM	2.7	3.1	2.9	2.9	3.3	2.2	1.9	2.5	2.2	2.8	2.9

Diastolic Blood Pressure - Atropine (mmHg)

	Time	PRE	30 MIN	1 HR	1:30 HR	2 HR	3 HR	4 HR	6 HR	8 HR	10 HR	12 HR
FOL	X	67.3	73.5	72.8	73.5	72.0	69.7	63.9	57.3	60.6	61. 3	60.4
	SEM	2.5	2.5	2.7	2.5	2.7	2.4	1.5	1.7	1.3	1.8	1.7
OVU	X	64.0	72.7	77.7	74.2	71.5	69.7	67.2	61.3	59.3	59.9	60.0
	SEM	1.3	2.6	2.1	2.2	2.0	2.5	3.0	1.4	1.3	1.2	1.8
LUT	X	65.0	71.8	68.3	66.7	72.7	65.5	59.1	60.0	57.5	61.1	60.3
	SEM	1.9	3.4	2.4	2.8	3.0	3.7	2.4	1.5	1.6	3.6	2.0

Table 26: Glucose Concentration - Atropine (µg/ml)

	Time	PRE	30 MIN	1 HR	2 HR	4 HR	8 HR
FOL	X	4.3	4.0	4.0	4.2	4.3	4.9
	SEM	0.2	0.2	0.1	0.1	0.1	0.2
OVU	X	4.2	4.0	4.1	4.1	4.3	5.0
	SEM	0.2	0.2	0.2	0.1	0.1	0.2
LUT	X	4.2	3.7	3.8	4.0	4.2	4.8
	SEM	0.2	0.2	0.2	0.1	0.1	0.1

Free Fatty Acid - Atropine (mmol)

	Time	PRE	30 HR	1 HR	2 HR	4 HR	8 HR
FOL	X	0.3	0.3	0.4	0.4	0.4	0.3
	SEM	0.0	0.0	0.0	0.0	0.0	0.0
OVU	X	0.3	0.4	0.4	0.4	0.4	0.3
	SEM	0.0	0.0	0.0	0.0	0.0	0.0
LUT	X	0.3	0.4	0.4	0.4	0.4	0.3
	SEM	0.0	0.0	0.0	0.0	0.0	0.0

Table 27: Hematocrit - Atropine (%)

	Time	PRE	30 HR	1 HR	2 HR	4 HR	8 HR
FOL	X	33.8	34.4	34.5	35.0	34.3	33.0
	SEM	1.0	0.8	1.1	1.1	1.0	0.5
OVU	X	34.3	34.9	34.9	35.0	35.0	33.2
	SEM	0.9	0.8	1.0	1.0	1.0	1.0
LUT	X	35.3	35.2	35.1	34.4	35.0	33.3
	SEM	0.9	1.0	1.0	1.0	0.9	0.8

Hemoglobin - Atropine (g/dL)

	Time	PRE	30 HR	1 HR	2 HR	4 HR	8 HR
FOL	X	11.9	12.0	11.9	12.1	11.9	12.1
	SEM	0.4	0.4	0.4	0.4	0.4	0.7
OVU	X	12.0	12.0	12.1	12.5	12.1	11.9
	SEM	0.4	0.4	0.5	0.7	0.7	0.6
LUT	X	12.3	11.9	11.9	12.0	11.8	12.1
	SEM	0.4	0.4	0.4	0.4	0.4	0.5

Table 28: Plasma Protein - Atropine (mg %)

	Time	PRE	30 HR	1 HR	2 HR	4 HR	8 HR
FOL	X	38.3	38.0	38.6	38.3	37.3	37.1
	SEM	0.5	0.7	0.6	0.7	0.4	0.5
OVU	X	38.5	38.3	38.5	38.4	38.7	36.9
	SEM	0.7	0.4	0.5	0.4	0.7	0.5
LUT	X	39.9	39.3	39.3	38.8	38.2	37.7
	SEM	0.6	0.7	0.7	0.7	0.6	0.6

Plasma Volume Change - Atropine - % Change

	Time	30 MIN	1 HR	2 HR	4 HR	8 HR
FOL	X	-1.0	0.6	-0.5	0.9	1.4
	SEM	-2.3	2.5	3.0	2.2	4.0
OVU	X	-0.8	-1.1	-3.0	1.5	4.9
	SEM	2.0	-2.7	-3.0	4.1	3.5
LUT	X	3.6	3.6	4.2	4.4	5.1
	SEM	1.4	1.4	2.2	3.9	2.9

Table 29: Sodium - Atropine (mEq/L)

	Time	PRE	30 HR	1 HR	2 HR	4 HR	8 HR
FOL	X	135.9	135.9	135.9	135.2	136.1	136.8
	SEM	1.0	1.0	0.9	0.9	0.9	0.9
OVU	X	136.1	135.5	136.0	135.6	136.4	135.8
	SEM	0.8	0.8	0.5	0.7	1.3	0.8
LUT	X	136.3	136.7	136.3	135.8	136.7	136.8
	SEM	1.3	1.3	1.4	1.1	1.4	1.5

Potassium - Atropine (mEq/L)

	Time	PRE	30 HR	1 HR	2 HR	4 HR	8 HR
FOL	X	3.6	3.7	3.8	3.9	3.8	3.7
	SEM	0.1	0.1	0.1	0.1	0.1	0.1
OVU	X	3.5	3.7	3.8	3.8	3.9	3.8
	SEM	0.1	0.1	0.1	0.1	0.1	0.1
LUT	X	3.6	3.8	3.9	3.8	3.7	3.8
	SEM	0.1	0.1	0.1	0.1	0.1	0.1

Osmolality - Atropine (mOsm/Kg)

	Time	PRE	30 HR	1 HR	2 HR	4 HR	8 HR
FOL	X	280.4	281.6	280.3	279.5	280.4	281.6
	SEM	1.6	1.5	1.2	1.6	1.5	1.7
OVU	X	280.6	279.7	278.4	280.2	281.3	280.3
	SEM	1.0	0.8	1.1	0.8	1.4	1.1
LUT	X	279.6	278.6	278.7	278.4	278.0	279.7
	SEM	1.6	1.4	1.2	1.4	1.1	1.4

Table 30: Serial +/- Accuracy -Atropine (%)

	Time	PRE	1 HR	2 HR	4HR	6 HR	8 HR	10 HR	12 HR
FOL	X	96.0	95.3	95.8	97.0	96.0	96.7	98.5	98.2
	SEM	1.2	1.6	1.4	0.8	0.9	1.2	0.5	0.8
OVU	X	95.7	94.8	94.5	96.2	96.7	97.3	95.7	97.3
	SEM	1.7	1.1	1.7	1.4	0.8	0.9	1.2	0.6
LUT	X	95.3	94.5	96.0	96.8	95.3	96.5	97.7	98.2
	SEM	1.2	1.4	1.0	0.8	1.9	1.1	1.0	0.7

Serial +/- Speed-Atropine (resp/min)

	Time	PRE	1 HR	2 HR	4HR	6 HR	8 HR	10 HR	12 HR
FOL	X	116.0	116.1	118.2	120.9	117.5	113.9	121.0	121.9
	SEM	23.0	24.5	21.4	19.2	20.0	18.4	21.2	18.8
OVU	X	108.2	106.3	111.2	116.5	122.0	115.1	122.8	124.5
	SEM	17.6	22.5	21.3	20.1	22.7	17.6	22.2	17.8
LUT	X	113.3	116.1	119.7	127.2	112.5	117.1	117.1	121.8
	SEM	23.8	20.9	21.2	23.8	17.9	20.9	22.9	22.1

Serial +/- Throughput- Atropine (speed*accuracy)

	Time	PRE	1 HR	2 HR	4HR	6 HR	8 HR	10 HR	12 HR
FOL	X	113.1	112.2	114.4	117.6	113.8	110.5	118.7	120.3
	SEM	23.4	24.8	21.7	19.0	20.3	18.4	20.4	19.0
OVU	X	104.2	101.5	106.8	112.9	118.4	112.5	119.3	121.5
	SEM	17.4	22.2	21.2	20.4	22.2	17.1	22.7	17.5
LUT	X	109.7	111.5	115.9	124.2	108.4	113.5	115.0	125.6
	SEM	23.6	21.0	21.1	24.0	18.4	20.3	22.6	22.5

Table 31: Choice Reaction Accuracy - Atropine (%)

	Time	PRE	1 HR	2 HR	4HR	6 HR	8 HR	10 HR	12 HR
FOL	X	99.3	97.5	99.3	98.7	98.5	97.7	98.7	98.2
	SEM	0.4	0.7	0.3	0.5	0.6	0.6	0.5	0.4
OVU	X	99.2	97.8	96.7	98.0	98.3	99.0	97.5	98.7
	SEM	1.3	1.9	1.9	2.2	2.1	1.5	2.7	1.9
LUT	X	97.7	98.0	97.7	99.2	97.5	98.3	99.3	97.8
	SEM	0.6	0.8	0.6	0.5	0.7	0.6	0.4	0.7

Choice Reaction Speed - Atropine (resp/min)

	Time	PRE	1 HR	2 HR	4HR	6 HR	8 HR	10 HR	12 HR
FOL	X	106.7	103.1	104.0	104.7	103.4	106.6	106.7	108.0
	SEM	5.0	5.7	4.1	4.0	4.6	4.6	4.9	4.0
OVU	X	102.5	100.8	96.5	100.0	104.8	106.0	107.4	107.6
	SEM	4.1	4.3	5.8	4.3	4.2	4.2	4.1	3.7
LUT	X	105.3	100.5	103.7	101.9	96.7	106.0	106.0	107.1
	SEM	4.7	4.8	4.0	4.6	6.5	4.3	4.3	4.0

Choice Reaction Throughput - Atropine (speed*accuracy)

	Time	PRE	1 HR	2 HR	4HR	6 HR	8 HR	10 HR	12 HR
FOL	X	105.9	100.8	103.3	103.4	102.0	104.1	105.5	106.0
	SEM	5.0	5.9	4.2	4.1	4.7	4.5	4.7	3.8
OVU	X	101.5	98.7	93.5	98.2	103.0	104.9	104.6	106.1
	SEM	3.9	4.5	5.9	4.6	4.2	4.1	3.9	3.6
LUT	X	102.0	98.4	101.4	101.1	94.3	104.3	105.3	105.3
	SEM	4.4	4.6	4.3	4.6	6.4	4.4	4.3	3.9

Table 32: Logical Reasoning - Accuracy - Atropine (%)

	Time	PRE	1 HR	2 HR	4HR	6 HR	8 HR	10 HR	12 HR
FOL	X	94.8	92.5	93.2	93.8	94.0	96.9	95.0	96.0
	SEM	2.2	2.0	2.8	2.6	1.8	1.6	1.5	2.2
OVU	X	94.8	95.1	93.0	94.3	94.3	94.9	94.3	95.3
	SEM	2.0	2.1	2.6	2.2	2.1	2.0	2.0	1.9
LUT	X	94.0	92.2	92.5	96.4	93.5	95.1	94.5	95.2
	SEM	2.1	2.6	2.6	2.8	1.9	1.9	1.7	2.0

Logical Reasoning - Speed - Atropine (resp/min)

	Time	PRE	1 HR	2 HR	4HR	6 HR	8 HR	10 HR	12 HR
FOL	X	28.0	30.7	28.3	30.8	29.2	30.6	30.7	31.4
	SEM	3.7	4.7	3.3	4.3	3.7	3.9	4.5	4.1
OVU	X	27.8	27.9	26.8	30.4	30.6	29.4	30.5	30.3
	SEM	4.0	3.8	3.6	4.5	4.3	4.4	4.1	3.9
LUT	X	28.8	30.5	30.3	30.8	28.4	27.3	30.2	30.7
	SEM	3.8	4.3	4.8	4.5	4.2	3.3	4.2	4.4

Logical Reasoning - Throughput - Atropine (speed*accuracy)

	Time	PRE	1 HR	2 HR	4HR	6 HR	8 HR	10 HR	12 HR
FOL	X	26.8	28.9	26.8	29.5	27.8	29.9	29.5	30.6
	SEM	3.7	4.8	3.4	4.5	3.9	4.0	4.4	4.0
OVU	X	26.7	27.0	25.3	29.2	29.3	28.1	29.2	29.3
	SEM	4.0	3.8	3.6	4.7	4.3	4.2	4.1	4.0
LUT	X	27.3	28.7	28.9	30.2	27.1	28.8	29.1	29.8
	SEM	3.7	4.3	5.0	4.6	4.4	4.3	4.4	4.5

Table 33: Stroop Accuracy- Atropine (%)

	Time	PRE	1 HR	2 HR	4HR	6 HR	8 HR	10 HR	12 HR
FOL	X	98.1	96.4	96.2	97.6	96.7	97.9	97.9	97.9
	SEM	0.5	0.8	0.4	0.8	0.7	0.8	0.6	0.4
OVU	X	97.4	97.2	97.0	98.1	98.4	98.3	98.3	98.3
	SEM	0.5	0.6	1.3	0.5	0.6	0.7	0.5	0.6
LUT	X	98.3	96.7	97.2	95.8	98.4	98.1	97.9	99.0
	SEM	0.4	0.9	0.6	1.0	0.5	0.9	0.6	0.5

Stroop Speed - Atropine (resp/min)

	Time	PRE	1 HR	2 HR	4HR	6 HR	8 HR	10 HR	12 HR
FOL	X	143.3	139.6	135.0	134.6	133.9	151.7	151.6	148.9
	SEM	8.4	6.4	7.6	6.3	7.8	11.7	9.8	7.8
OVU	X	139.8	138.4	133.2	138.2	143.1	146.1	149.2	152.3
	SEM	10.1	8.5	7.6	10.0	9.7	10.4	8.5	9.6
LUT	X	140.9	148.4	137.7	131.7	135.1	140.4	148.5	153.1
	SEM	8.4	10.1	7.3	8.0	10.2	6.7	10.4	7.8

Stroop Throughput - Atropine (speed*accuracy)

	Time	PRE	1 HR	2 HR	4HR	6 HR	8 HR	10 HR	12 HR
FOL	X	140.4	134.4	116.2	131.2	129.3	148.8	148.4	146.0
	SEM	8.0	5.9	10.4	6.0	7.3	11.8	9.7	7.8
OVU	X	136.1	134.6	129.7	135.4	141.3	143.6	146.6	149.7
	SEM	9.9	8.4	8.0	9.6	10.0	10.0	7.9	9.5
LUT	X	138.3	143.4	133.8	126.2	132.9	137.4	145.9	151.1
	SEM	8.0	9.7	7.1	7.6	9.9	6.1	9.9	7.6

Table 34: Manikin Accuracy - Atropine (%)

	Time	PRE	1 HR	2 HR	4HR	6 HR	8 HR	10 HR	12 H
FOL	X	97.9	95.8	96.9	97.9	97.9	97.4	98.4	96.4
	SEM	1.6	1.8	1.4	1.2	0.9	0.9	0.8	1.6
OVU	X	97.4	95.8	97.4	96.9	97.4	100.0	97.4	98.4
	SEM	2.6	1.4	1.2	1.2	1.2	0.0	1.2	0.8
LUT	X	97.4	95.8	95.8	97.9	97.4	93.2	100.0	96.9
	SEM	0.9	1.6	1.6	1.2	1.2	2.7	0.0	1.2

Manikin Speed - Atropine (%)

	Time	PRE	1 HR	2 HR	4HR	6 HR	8 HR	10 HR	12 H
FOL	X	63.4	63.6	58.7	62.9	61.4	63.2	62.2	66.6
	SEM	5.9	6.4	6.9	5.7	6.7	7.1	6.8	7.9
OVU	X	61.0	60.9	58.2	59.2	61.9	64.4	60.7	66.8
	SEM	7.3	8.0	7.1	7.1	6.7	7.4	7.3	7.5
LUT	X	65.6	62.2	63.0	63.9	62.2	63.2	60.1	65.4
	SEM	6.9	6.7	6.4	7.6	7.8	8.5	6.9	7.5

Manikin Throughput - Atropine (speed*accuracy)

	Time	PRE	1 HR	2 HR	4HR	6 HR	8 HR	10 HR	12 H
FOL	X	62.3	61.0	57.2	61.5	60.3	61.4	61.3	64.5
	SEM	6.0	6.3	7.0	5.6	6.7	6.8	6.7	7.9
OVU	X	60.2	58.2	56.7	57.4	60.3	64.4	59.5	65.6
	SEM	7.7	7.4	6.9	7.0	6.7	7.4	7.4	7.2
LUT	X	64.0	59.3	60.7	63.0	60.2	60.3	60.1	63.2
	SEM	6.2	6.3	6.4	7.8	7.2	8.9	6.9	7.1

Table 35: Sleep Scale -Atropine

	Time	PRE	1 HR	2 HR	4HR	6 HR	8 HR	10 HR	12 HR
FOL	X	2.4	4.2	4.3	3.7	3.4	3.3	2.9	2.6
	SEM	0.3	0.4	0.5	0.5	0.3	0.3	0.2	0.3
OVU	X	2.0	3.8	4.1	3.3	3.1	2.9	2.4	2.5
	SEM	0.3	0.4	0.5	0.4	0.4	0.3	0.3	0.4
LUT	X	1.8	3.2	3.9	3.7	3.5	3.2	2.9	2.3
	SEM	0.2	0.3	0.5	0.4	0.5	0.4	0.5	0.5

Table 36: POMS - Tension - Atropine

	Time	PRE	1 HR	2 HR	4HR	6 HR	8 HR	10 HR	12 HR
FOL	X	11.6	14.4	13.9	13.9	9.5	12.5	13.2	11.3
	SEM	4.3	4.3	4.5	4.8	3.7	4.2	4.6	4.6
OVU	X	9.4	12.0	13.4	11.3	12.5	12.0	11.8	13.9
	SEM	3.8	3.6	4.3	4.5	4.8	4.2	5.0	4.6
LUT	X	13.4	10.6	11.6	10.9	11.1	13.4	13.2	11.1
	SEM	5.8	5.3	4.2	4.7	4.7	5.7	4.6	3.9

POMS - Depression - Atropine

	Time	PRE	1 HR	2 HR	4HR	6 HR	8 HR	10 HR	12 HR
FOL	X	2.9	4.7	3.9	3.8	3.3	3.2	4.7	2.6
	SEM	2.0	2.8	1.8	1.6	1.9	1.7	2.4	1.5
OVU	X	2.2	2.4	2.5	3.1	2.8	2.9	2.1	1.4
	SEM	1.2	1.7	1.3	1.8	1.6	2.0	1.2	0.7
LUT	X	4.9	4.9	4.0	3.8	4.6	6.5	4.6	3.3
	SEM	4.4	3.5	2.9	2.4	2.8	4.4	2.5	2.9

POMS - Anger - Atropine

	Time	PRE	1 HR	2 HR	4HR	6 HR	8 HR	10 HR	12 HR
FOL	X	3.8	4.0	2.1	2.6	3.7	3.1	3.0	2.3
	SEM	2.7	2.8	1.6	1.6	2.6	2.2	2.0	1.6
OVU	X	3.0	3.1	3.3	3.3	3.7	3.0	3.1	2.4
	SEM	2.1	2.2	1.9	2.3	2.3	2.1	1.7	1.2
LUT	X	5.6	4.5	4.2	4.2	3.3	4.5	4.7	3.1
	SEM	4.7	4.0	3.0	3.2	2.2	3.8	3.2	2.1

Table 37: POMS - Vigor- Atropine

	Time	PRE	1 HR	2 HR	4HR	6 HR	8 HR	10 HR	12 HR
FOL	X	44.8	34.6	27.9	29.7	31.0	34.4	34.4	35.9
	SEM	7.5	7.5	6.0	5.8	7.1	6.4	7.6	6.6
OVU	X	48.7	35.7	28.1	32.8	36.5	35.7	36.2	39.8
	SEM	6.3	7.1	6.5	6.9	6.7	6.7	5.9	6.7
LUT	X	51.3	34.9	29.2	30.0	29.2	31.5	34.1	37.8
	SEM	6.1	5.2	6.3	6.5	5.2	6.3	6.6	6.3

POMS - Fatigue - Atropine

	Time	PRE	1 HR	2 HR	4HR	6 HR	8 HR	10 HR	12 HR
FOL	X	12.8	23.5	28.6	26.5	22.0	26.2	27.9	26.5
	SEM	4.6	6.5	6.9	6.4	5.1	5.5	5.9	4.9
OVU	X	10.7	19.9	23.2	21.7	22.3	24.9	23.8	24.7
	SEM	4.7	6.5	6.1	5.4	7.0	6.1	6.7	5.9
LUT	X	9.2	14.3	20.2	21.7	22.6	22.9	19.9	19.9
	SEM	5.0	5.5	6.2	5.6	4.8	5.6	5.6	5.6

POMS - Confusion - Atropine

	Time	PRE	1 HR	2 HR	4HR	6 HR	8 HR	10 HR	12 HR
FOL	X	13.1	18.4	16.9	19.3	14.6	16.9	19.9	15.8
	SEM	3.6	4.5	4.0	4.4	3.8	4.0	3.3	3.5
OVU	X	11.3	17.6	17.9	17.6	15.2	15.5	16.1	16.7
	SEM	3.8	4.3	3.7	4.3	4.9	4.0	4.8	4.1
LUT	X	11.3	19.9	20.8	19.9	18.1	16.4	16.8	16.9
	SEM	4.6	5.8	6.0	5.1	4.4	4.5	4.1	3.6

Table 38: Headache Scale - Atropine

FOL	X	1.8
	SEM	0.2
OVU	X	2.2
	SEM	0.3
LUT	X	2.3
	SEM	0.3

Table 39: Triazolam Concentration - Triazolam

	Time	PRE	15 min	30 min	45 min	1HR	1.5 HR	2HR	4 HR	6 HR	8 HR	10 HR
FOL	X	0.0	0.3	1.3	1.9	1.6	1.5	1.5	0.9	0.5	0.3	0.2
	SEM	0.0	0.1	0.2	0.4	0.2	0.1	0.2	0.1	0.1	0.1	0.0
OVU	X	0.0	0.2	0.8	1.2	1.3	1.5	1.6	0.9	0.6	0.3	0.1
	SEM	0.0	0.1	0.2	0.2	0.2	0.2	0.1	0.1	0.1	0.1	0.0
LUT	X	0.0	0.2	0.9	1.4	1.8	1.8	1.7	1.0	0.6	0.4	0.2
	SEM	0.0	0.1	0.2	0.2	0.2	0.1	0.1	0.1	0.1	0.1	0.0

Table 40: Epinephrine Concentration - Triazolam - (ug/mL)

	Time	PRE	30 MIN	1 HR	1:30 HR	2 HR	4 HR	6 HR	8 HR	10 HR
FOL	X	25.7	32.8	35.1	41.0	26.9	29.3	32.8	42.3	37.6
	SEM	7.7	6.4	12.3	7.5	7.1	8.6	7.2	12.8	7.0
OVU	X	55.9	68.8	54.2	37.3	35.1	54.7	33.1	53.1	44.6
	SEM	16.9	20.6	14.1	8.1	6.7	17.2	6.4	18.0	19.4
LUT	X	35.0	35.1	64.4	49.5	39.0	60.6	71.8	68.2	39.1
	SEM	15.9	13.4	24.1	18.2	16.0	27.7	37.5	44.0	6.8

Norepinephrine Concentration - Atropine - (ug/mL)

	Time	PRE	30 MIN	1 HR	1:30 HR	2 HR	4 HR	6 HR	8 HR	10 HR
FOL	X	199.8	181.0	166.2	167.5	204.9	208.7	146.3	157.2	150.3
	SEM	20.5	16.1	13.7	18.5	29.3	30.5	16.2	27.1	13.6
OVU	X	292.2	335.0	237.2	284.2	375.2	378.9	270.1	306.2	242.8
	SEM	35.2	75.6	34.5	72.4	118.6	81.0	44.7	110.0	66.7
LUT	X	341.7	315.2	309.7	241.4	366.1	407.1	293.4	229.7	228.3
	SEM	51.3	42.2	45.3	24.6	44.7	59.2	41.5	25.7	16.1

Table 41: Cortisol - Triazolam (mmol/L)

	Time	PRE	30 HR	1 HR	2 HR	4 HR	8 HR
FOL	X	373.2	197.3	162.5	182.6	212.7	148.5
	SEM	36.8	23.1	20.7	21.0	15.2	19.4
OVU	X	374.5	192.6	169.6	179.1	243.0	193.1
	SEM	34.3	20.7	26.8	25.3	17.3	26.9
LUT	X	376.5	191.1	146.7	133.7	214.2	185.1
	SEM	41.9	26.4	22.1	12.8	20.8	19.3

Table 42: Heart Rate - Triazolam (bpm)

	Time	PRE	30 MIN	1 HR	1:30 HR	2 HR	3 HR	4 HR	6 HR	8 HR	10 HR
FOL	X	66.6	67.3	62.1	63.0	66.4	72.8	68.0	68.1	66.8	68.6
	SEM	2.3	3.1	2.5	2.6	2.2	1.5	1.6	2.2	2.5	2.9
OVU	X	68.5	64.5	65.1	65.8	66.0	72.3	70.1	69.8	66.2	72.4
	SEM	2.6	2.5	2.3	1.7	1.8	2.4	2.5	2.3	2.9	3.9
LUT	X	72.1	67.5	66.8	67.6	68.7	70.8	74.7	71.0	73.8	74.9
	SEM	3.0	3.7	2,9	3.0	3.5	3.3	3.5	3.4	3.1	3.4

Rate Pressure Product - Triazolam ((SBP*HR)/100)

	Time	PRE	30 MIN	1 HR	1:30 HR	2 HR	3 HR	4 HR	6 HR	8 HR	10 HR
FOL	X	70.0	69.0	63.8	63.1	65.0	73.1	65.8	66.5	64.8	69.3
	SEM	4.0	4.1	3.0	3.0	2.7	3.4	2.2	2.7	2.5	2.7
OVU	X	76.9	66.7	66.5	66.9	67.5	72.9	70.2	70.5	66.4	72.8
	SEM	3.0	3.1	2.7	2.4	2.3	3.4	2.6	2.8	3.6	4.4
LUT	X	77.1	70.1	64.5	69.8	70.5	73.4	75.1	68.9	74.1	74.1
	SEM	3.1	4.6	3.7	4.6	4.5	5.1	4.1	3.9	3.7	3.2

Table 43: Systolic Blood Pressure - Triazolam - (mmHg)

	Time	PRE	30 MIN	1 HR	1:30 HR	2 HR	3 HR	4 HR	6 HR	8 HR	10 HR
FOL	X	104.3	102.2	102.8	100.2	97.8	99.8	96.6	97.5	97.8	101.2
	SEM	2.9	2.4	2.3	2.2	1.6	2.4	1.8	1.6	1.9	1.8
OVU	X	112.5	107.5	101.6	101.5	102.4	100.8	100.3	100.9	100.1	100.4
	SEM	2.3	2.5	2.6	2.1	2.4	2.8	1.9	2.2	2.1	2.3
LUT	X	107.5	103.6	96.5	102.5	100.5	103.3	100.4	96.7	100.2	99.5
	SEM	2.8	3.3	3.9	3.2	2.2	3.0	1.6	1.5	2.0	1.4

Diastolic Blood Pressure - Triazolam - (mmHg)

	Time	PRE	30 MIN	1 HR	1:30 HR	2 HR	3 HR	4 HR	6 HR	8 HR	10 HR
FOL	X	63.4	67.5	64.3	64.2	63.3	62.7	60.5	61.2	61.8	64.3
	SEM	1.7	1.5	1.6	1.3	1.5	1.5	1.5	1.5	1.7	2.7
OVU	X	70.4	67.5	65.8	64.4	65.8	61.2	61.3	59.2	59.3	58.4
	SEM	2.7	1.5	1.5	1.8	1.7	2.0	1.6	1.7	1.6	1.8
LUT	X	66.0	66.5	63.2	61.8	64.4	59.8	58.6	58.0	59.8	59.5
	SEM	2.2	2.1	2.6	1.7	2.4	3.3	1.0	1.5	1.9	1.4

Table 44: Hematocrit - Triazolam (%)

	Time	PRE	30 HR	1 HR	2 HR	4 HR	8 HR
FOL	X	33.3	32.1	32.7	33.6	32.2	30.7
	SEM	0.9	1.1	1.0	1.1	1.1	0.9
OVU	X	35.1	33.1	33.4	33.9	32.6	31.2
	SEM	1.2	1.3	1.0	1.1	1.0	1.0
LUT	X	35.0	33.7	33.7	34.4	32.6	32.5
	SEM	1.0	1.1	1.1	1.2	1.2	1.0

Hemoglobin - Triazolam (g/dL)

	Time	PRE	30 HR	1 HR	2 HR	4 HR	8 HR
FOL	X	11.1	11.2	11.2	11.4	11.3	11.2
	SEM	0.5	0.6	0.6	0.6	0.5	0.4
OVU	X	11.9	11.4	11.3	11.9	11.5	11.5
	SEM	0.5	0.5	0.5	0.5	0.5	0.5
LUT	X	12.0	11.3	12.3	11.5	11.7	11.4
	SEM	0.7	0.5	1.0	0.6	0.9	0.5

Table 45: Plasma Protein - Triazolam (mg %)

	Time	PRE	30 HR	1 HR	2 HR	4 HR	8 HR
FOL	X	38.2	37.1	37.1	37.6	37.1	37.3
	SEM	0.6	0.4	0.5	0.5	0.5	0.7
OVU	X	38.9	37.0	37.5	38.3	37.5	36.8
	SEM	0.6	0.5	0.5	0.7	0.5	0.4
LUT	X	39.0	37.7	37.5	38.4	38.0	37.3
	SEM	0.5	0.5	0.5	0.5	0.6	0.4

Plasma Volume Change - Triazolam - % Change

	Time	30 MIN	1 HR	2 HR	4 HR	8 HR
FOL	X	-0.3	0.2	-5.8	-0.8	0.8
	SEM	-2.2	1.9	-2.1	-2.9	3.8
OVU	X	7.4	8.4	2.0	7.5	9.3
	SEM	1.4	2.3	1.8	1.6	2.6
LUT	X	8.3	1.7	5.7	9.4	9.1
	SEM	3.2	3.2	2.6	5.2	2.8

Table 46: Serial +/- Accuracy -Triazolam (%)

	Time	PRE	1:30 HR	3 HR	6 HR	10 HR
FOL	X	96.5	89.8	96.7	97.3	98.0
	SEM	1.2	4.0	1.9	0.8	0.7
OVU	X	95.8	90.5	93.6	97.1	96.5
	SEM	1.4	1.9	1.5	1.2	0.7
LUT	X	96.2	89.6	94.6	96.2	97.6
	SEM	1.3	3.7	2.1	1.2	0.7

Serial +/- Speed-Triazolam (resp/min)

	Time	PRE	1:30 HR	3 HR	6 HR	10 HR
FOL	X	104.4	77.4	107.0	126.4	129.2
	SEM	19.3	16.7	22.1	26.5	27.3
OVU	X	115.6	92.1	106.5	125.5	129.7
	SEM	21.7	25.5	28.0	27.0	26.8
LUT	X	119.5	92.3	99.9	121.5	127.1
	SEM	26.2	30.1	23.2	24.6	29.9

Serial +/- Throughput-Triazolam (speed*accuracy)

	Time	PRE	1:30 HR	3 HR	6 HR	10 HR
FOL	X	101.9	72.7	105.3	123.7	127.3
	SEM	19.3	16.5	22.3	26.6	27.4
OVU	X	111.9	86.6	100.3	126.6	125.9
	SEM	21.2	25.4	26.4	26.1	26.5
LUT	X	116.9	87.4	96.4	118.3	124.9
	SEM	26.6	29.9	22.6	24.7	30.1

Table 47: Choice Reaction - Accuracy - Triazolam (%)

	Time	PRE	1:30 HR	3 HR	6 HR	10 HR
FOL	X	98.7	95.5	97.3	98.5	99.3
	SEM	0.5	1.4	1.1	0.5	0.4
OVU	X	98.4	96.9	98.6	96.5	98.7
	SEM	0.5	0.8	0.5	1.6	0.5
LUT	X	97.8	97.3	97.6	98.7	98.5
	SEM	0.6	0.7	0.7	0.5	0.5

Choice Reaction - Speed - Triazolam (resp/min)

	Time	PRE	1:30 HR	3 HR	6 HR	10 HR
FOL	X	104.9	89.7	94.6	104.5	108.1
	SEM	4.2	6.4	7.4	4.4	4.2
OVU	X	108.2	94.9	97.9	105.4	111.3
	SEM	5.1	7.7	6.2	5.0	4.9
LUT	X	109.7	93.3	101.6	107.1	110.8
	SEM	5.3	8.0	7.1	5.1	5.0

Choice Reaction Throughput - Triazolam (speed*accuracy)

	Time	PRE	1:30 HR	3 HR	6 HR	10 HR
FOL	X	103.5	86.4	92.5	102.9	107.3
	SEM	4.2	6.8	7.7	4.3	4.1
OVU	X	106.6	92.3	96.6	104.4	109.9
	SEM	5.3	7.5	6.3	4.4	4.6
LUT	X	107.5	91.0	99.4	105.8	109.2
	SEM	5.6	8.0	7.2	5.1	5.1

Table 48: Logical Reasoning - Accuracy -Triazolam (%)

	Time	PRE	1:30 HR	3 HR	6 HR	10 HR
FOL	X	95.0	88.0	95.4	94.3	89.3
	SEM	3.6	3.9	1.9	3.0	4.3
OVU	X	95.3	92.9	93.2	86.6	93.5
	SEM	2.9	2.3	2.6	7.0	2.6
LUT	X	92.9	91.4	89.5	92.3	94.9
	SEM	3.3	3.5	3.1	2.7	2.7

Logical Reasoning - Speed -Triazolam (resp/min)

	Time	PRE	1:30 HR	3 HR	6 HR	10 HR
FOL	X	28.0	21.3	26.1	26.1	28.0
	SEM	4.3	3.5	4.2	4.2	4.4
OVU	X	30.8	23.4	25.4	27.3	27.6
	SEM	5.5	4.6	5.3	5.1	4.6
LUT	X	30.0	25.0	27.4	28.8	29.8
	SEM	4.9	4.7	4.2	4.7	4.8

Logical.Reasoning - Throughput - Triazolam (speed*accuracy)

	Time	PRE	1:30 HR	3 HR	6 HR	10 HR
FOL	X	35.0	27.1	33.6	33.0	34.6
	SEM	8.0	9.7	8.2	8.1	7.1
OVU	X	29.8	22.2	24.4	33.2	26.2
	SEM	5.6	4.6	5.5	8.4	4.5
LUT	X	28.7	23.8	25.4	27.3	28.9
	SEM	5.0	4.9	4.2	4.9	5.0

Table 49: Stroop Accuracy - Triazolam (%)

	Time	PRE	1:30 HR	3 HR	6 HR	10 HR
FOL	X	97.9	95.3	96.0	97.0	98.4
	SEM	0.9	1.3	0.9	0.6	0.5
OVU	X	97.7	96.0	96.7	99.9	97.3
	SEM	0.7	0.8	0.7	3.5	0.6
LUT	X	98.1	96.2	96.1	97.5	98.7
	SEM	0.6	1.0	1.0	1.0	0.8

Stroop Speed - Triazolam (resp/min)

	Time	PRE	1:30 HR	3 HR	6 HR	10 HR
FOL	X	142.2	123.5	131.7	138.5	141.3
	SEM	11.3	11.6	12.6	8.6	8.1
OVU	X	146.7	132.3	123.9	135.9	150.0
	SEM	10.1	10.3	8.1	7.8	9.6
LUT	X	141.6	127.8	133.6	141.5	144.5
	SEM	10.1	11.7	10.4	11.7	9.0

Stroop Throughput- Triazolam (speed*accuracy)

	Time	PRE	1:30 HR	3 HR	6 HR	10 HR
FOL	X	139.6	118.4	127.2	134.3	139.1
	SEM	11.4	11.5	12.5	8.3	8.0
OVU	X	143.1	127.4	119.6	129.4	146.4
	SEM	9.7	10.2	7.5	8.0	9.6
LUT	X	138.8	123.6	128.7	137.8	142.6
	SEM	9.7	11.9	10.9	11.4	9.0

Table 50: Manikin Accuracy - Triazolam (%)

	Time	PRE	1:30 HR	3 HR	6 HR	10 HR
FOL	X	99.0	93.4	95.5	99.0	98.4
	SEM	1.4	3.1	2.2	0.7	0.8
OVU	X	96.9	94.9	94.4	88.9	98.3
	SEM	1.3	2.2	2.4	5.2	1.2
LUT	X	97.7	96.0	94.4	98.3	99.4
	SEM	1.0	2.1	1.4	1.2	0.6

Manikin Speed- Triazolam (resp/min)

	Time	PRE	1:30 HR	3 HR	6 HR	10 HR
FOL	X	61.5	54.1	51.4	59.0	63.5
	SEM	7.0	6.9	7.5	6.8	6.4
OVU	X	62.7	54.8	57.7	62.5	62.7
	SEM	6.9	7.8	8.1	7.4	6.5
LUT	X	62.8	53.4	57.5	65.2	64.4
	SEM	7.0	8.5	8.7	7.1	8.0

Manikin Throughput -Triazolam (speed*accuracy)

	Time	PRE	1:30 HR	3 HR	6 HR	10 HR
FOL	X	60.2	48.3	48.6	58.6	65.7
	SEM	7.1	6.8	6.4	6.9	6.5
OVU	X	60.6	59.7	62.0	54.9	61.9
	SEM	6.6	10.3	10.0	7.9	6.7
LUT	X	63.4	51.7	54.0	63.5	63.7
	SEM	7.8	8.5	8.4	6.8	7.6

Table 51: Sleep Scale-Triazolam

	Time	PRE	1:30 HR	3 HR	6 HR	10 HR
FOL	X	2.3	3.5	2.9	2.3	1.8
	SEM	0.4	0.5	0.4	0.3	0.3
OVU	X	1.7	3.5	2.8	2.2	1.7
	SEM	0.3	0.5	0.3	0.2	0.1
LUT	X	2.0	3.5	2.9	2.5	2.4
	SEM	0.3	0.4	0.3	0.3	0.2

Table 52: POMS - Tension - Triazolam

	Time	PRE	1:30 HR	3 HR	6 HR	10 HR
FOL	X	7.4	7.6	8.8	6.5	6.7
	SEM	3.6	2.2	3.6	3.1	3.6
OVU	X	8.3	9.8	8.1	10.1	9.6
	SEM	3.2	3.1	3.2	2.7	3.4
LUT	X	10.6	11.1	13.3	8.6	9.1
	SEM	4.8	3.8	4.0	3.9	3.9

POMS - Depression - Triazolam

	Time	PRE	1:30 HR	3 HR	6 HR	10 HR
FOL	X	1.5	1.5	1.4	1.0	1.5
	SEM	1.0	0.6	0.7	0.8	0.8
OVU	X	2.0	2.1	2.5	2.7	2.0
	SEM	1.0	1.1	1.4	1.1	1.1
LUT	X	3.0	2.9	2.0	1.7	1.8
	SEM	2.1	1.3	1.6	1.2	0.9

POMS - Anger - Triazolam

	Time	PRE	1:30 HR	3 HR	6 HR	10 HR
FOL	X	1.2	1.9	1.3	0.7	1.2
	SEM	1.0	1.1	0.9	0.7	0.8
OVU	X	1.0	2.8	2.1	0.6	1.3
	SEM	0.8	1.4	1.1	0.3	0.7
LUT	X	3.4	3.2	2.7	2.1	1.5
	SEM	2.8	1.9	1.8	1.9	0.9

Table 53: POMS - Vigor-Triazolam

	Time	PRE	1:30 HR	3 HR	6 HR	10 HR
FOL	X	50.5	34.1	42.3	44.0	43.8
	SEM	8.1	8.8	7.7	8.0	7.9
OVU	X	44.1	35.5	35.3	40.9	45.2
	SEM	8.1	8.0	8.9	8.5	7.9
LUT	X	50.0	35.8	42.5	44.9	43.6
	SEM	7.6	7.8	8.1	9.0	9.0

POMS - Fatigue - Triazolam

	Time	PRE	1:30 HR	3 HR	6 HR	10 HR
FOL	X	17.3	25.0	17.2	18.9	15.8
	SEM	5.1	5.4	4.3	5.9	6.3
OVU	X	11.8	17.5	13.9	11.7	14.6
	SEM	4.2	5.3	4.6	4.3	4.4
LUT	X	16.2	20.4	14.3	17.5	17.2
	SEM	6.8	7.3	6.0	5.5	5.2

POMS - Confusion - Triazolam

	Time	PRE	1:30 HR	3 HR	6 HR	10 HR
FOL	X	10.4	20.2	13.6	11.6	11.6
	SEM	2.9	3.8	4.1	3.8	3.1
OVU	X	15.0	16.6	11.8	11.4	12.7
	SEM	3.2	4.1	3.8	3.5	3.5
LUT	X	16.6	18.5	9.9	12.7	13.3
	SEM	5.1	5.0	3.6	3.4	3.9

Table 54: ICG Concentration (µg/ml)

	Time	PRE	5 min	10 min	15 min	20 min	30 min
FOL	$\bar{X}$	0.00	6.60	1.52	0.38	0.15	0.12
	SEM	0.00	5.06	1.52	0.53	0.37	0.33
OVU	$\bar{X}$	0.00	4.70	1.34	0.38	0.02	0.02
	SEM	0.00	1.12	0.76	0.48	0.06	0.03
LUT	$\bar{X}$	0.00	4.70	1.22	0.30	0.68	0.02
	SEM	0.00	1.02	0.75	0.31	0.10	0.05